

Merlin G. Butler  
Phillip D.K. Lee  
Barbara Y. Whitman *Editors*

# Management of Prader-Willi Syndrome



Third Edition

 Springer

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*La Monstrua vestida*



*La Monstrua desnuda*

These paintings by the Spanish baroque court painter Juan Carreño de Miranda (1616-1685) depict Doña Eugenia Martínez Vallejo at approximately 6 years of age (c. 1680), after she was brought to the court of Charles II of Spain and given the moniker “La Monstrua.” It is said that upon viewing these paintings in the Museo del Prado, Madrid, Dr. Andrea Prader immediately recognized features consistent with Prader-Willi syndrome. Although we may never know if this child did in fact have PWS, the paintings and contemporaneous 17th century descriptions of her condition strongly support this supposition. Indeed, these paintings are often regarded as the earliest illustrations of PWS. La Monstrua has continued to be an intriguing figure, as evidenced by an outdoor sculpture in Avilés created in 1997 by the Spanish artist Amado González Hevia “Favila” (b. 1954; [www.amadofavila.com](http://www.amadofavila.com)) based on these baroque portraits.

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**Merlin G. Butler, MD, PhD**

*Chief, Section of Medical Genetics and Molecular Medicine, William R. Brown/Missouri Chair of Medical Genetics and Molecular Medicine;  
Professor of Pediatrics, University of Missouri-Kansas City School of  
Medicine, Children's Mercy Hospitals and Clinics, Kansas City,  
Missouri*

**Phillip D.K. Lee, MD**

*Chief Scientific Officer, Immunodiagnostic Systems Ltd., Bordon, Tyne and  
Wear, United Kingdom*

**Barbara Y. Whitman, PhD**

*Professor of Pediatrics, Saint Louis University School of Medicine, Cardinal  
Glennon Children's Hospital, St. Louis, Missouri*

Editors

With 125 Illustrations, 11 in Full Color



**Springer**

Merlin G. Butler, MD, PhD  
Chief, Section of Medical Genetics  
and Molecular Medicine  
William R. Brown/Missouri  
Chair of Medical Genetics and  
Molecular Medicine

*and*

Professor of Pediatrics  
University of Missouri-Kansas  
City School of Medicine  
Children's Mercy Hospitals  
and Clinics  
Kansas City, MO 64108  
USA

Phillip D.K. Lee, MD  
Chief Scientific Officer  
Immunodiagnostic Systems Ltd.  
Boldon, Tyne and Wear  
NE 35 9PD  
UK

Barbara Y. Whitman, PhD  
Professor of Pediatrics  
Saint Louis University School  
of Medicine  
Cardinal Glennon Children's Hospital  
St. Louis, MO 63104  
USA

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# Contributors

*Randell C. Alexander, MD, PhD*

Professor of Clinical Pediatrics, Morehouse School of Medicine,  
Department of Pediatrics, Atlanta, GA 30310, USA

*Karin Buiting, PhD*

Institut für Humangenetik, Universitätsklinikum Essen, Essen,  
Germany

*Merlin G. Butler, MD, PhD*

Chief, Section of Medical Genetics and Molecular Medicine, William R.  
Brown/Missouri Chair of Medical Genetics and Molecular Medicine;  
Professor of Pediatrics, University of Missouri-Kansas City School of  
Medicine, Children's Mercy Hospitals and Clinics, Kansas City, MO  
64108, USA

*Aaron L. Carrel, MD*

Associate Professor of Pediatrics, University of Wisconsin Medical  
School, Madison, WI 53792, USA

*Suzanne B. Cassidy, MD*

Clinical Professor of Pediatrics, University of California, Irvine, Orange,  
CA 92868, USA

*Naomi Chedd, MS, LMHC*

Education Consultant and Mental Health Counselor in private  
practice, Brookline, MA 02446, USA

*Steve Drago, BS, CABA*

Associate Director, ARC of Alachua County, Gainesville, FL 32606,  
USA

*Urs Eiholzer, MD*

Director, Institute Growth Puberty Adolescence, Zürich, Switzerland

*Pamela F. Eisen*

President, International Prader-Willi Syndrome Organization (IPWSO),  
Wormleysburg, PA 17043, USA

*Kenneth J. Ellis, PhD*

Professor of Pediatrics and Director, Body Composition Laboratory,  
Children's Nutrition Research Center, Baylor College of Medicine,  
Houston, TX 77030, USA

*Giorgio Fornasier*

Director of Program Development, International Prader-Willi Syndrome Organization (IPWSO), 32020 Limana, Italy

*Janice L. Forster, MD*

Former Consulting Psychiatrist, The Children's Institute Prader-Willi Syndrome and Behavior Disorders Program; Physician in private practice, Pittsburgh, PA 15228, USA

*Toni Goelz, BS*

Staff Physical Therapist, Cardinal Glennon Children's Hospital, St. Louis, MO 63104, USA

*Barbara J. Goff, EdD*

Consultant for Prader-Willi Syndrome; Assistant Professor of Education, Westfield State College, Westfield, MA 01086, USA

*Linda M. Gourash, MD*

Formerly Chief Attending Physician, The Children's Institute Prader-Willi Syndrome and Behavior Disorders Program; Physician in private practice, Pittsburgh, PA 15228, USA

*Louise R. Greenswag, RN, PhD*

Consultant for Prader-Willi Syndrome, Division of Developmental and Behavioral Medicine, Center for Disabilities and Development, University of Iowa Hospitals and Clinics, Iowa City, IA 52242, USA

*James E. Hanchett, MD<sup>†</sup>*

Formerly Consultant to The Children's Institute Prader-Willi Syndrome and Behavior Disorders Program, Pittsburgh, PA 15217, USA

*Jeanne M. Hanchett, MD*

Assistant Professor, Department of Pediatrics, University of Pittsburgh School of Medicine; The Children's Institute of Pittsburgh, Pittsburgh, PA 15217, USA

<sup>†</sup> Deceased.

*Janalee Heinemann, MSW*

Executive Director, Prader-Willi Syndrome Association (USA),  
Sarasota, FL 34242, USA

*Robert M. Hodapp, PhD*

Co-Director, Family Research Program, Vanderbilt Kennedy Center;  
Professor, Special Education, Peabody College, Nashville, TN 37203,  
USA

*Bernhard Horsthemke, PhD*

Professor of Human Genetics, Institut für Humangenetik, Universitäts-  
klinikum Essen, Essen, Germany

*Kevin Jackson, PhD, BCBA*

Senior Behavior Analyst, Agency for Persons with Disabilities,  
Gainesville, FL 32602, USA

*Ellie Kazemi*

Graduate Student, Psychological Studies in Education, University of  
California, Los Angeles, Graduate School of Education and Information  
Studies, Los Angeles, CA 90095, USA

*Phillip D.K. Lee, MD*

Formerly Professor of Pediatrics, David Geffen School of Medicine at  
University of California, Los Angeles (UCLA), Los Angeles, CA 90095,  
USA; currently Chief Scientific Officer, Immunodiagnostic Systems  
Ltd., Boldon, Tyne and Wear, NE 35 9PD, UK

*Karen Levine, PhD*

Clinical Director, Autism Services, North Shore ARC, Danvers, MA  
01923, USA

*Barbara A. Lewis, PhD, CCC-SLP*

Associate Professor, Department of Pediatrics, School of Medicine,  
Case Western Reserve University, Rainbow Babies and Children's  
Hospital, Cleveland, OH 44106, USA

*Shawn E. McCandless, MD*

Assistant Professor, Genetics and Pediatrics, Center for Human  
Genetics, University Hospitals of Cleveland and Case Western Reserve  
University, Cleveland, OH 44106, USA

*Harriette R. Mogul, MD, MPH*

Professor of Medicine, Chief, Section of Obesity and Osteoporosis,  
Department of Medicine, New York Medical College, Valhalla, NY  
10595, USA

*Kristin G. Monaghan, PhD*

Director, DNA Diagnostic Laboratory, Department of Medical Genetics,  
Henry Ford Hospital and Medical Center, Detroit, MI 48202, USA

*Ann O. Scheimann, MD*

Assistant Professor of Pediatrics, Johns Hopkins School of Medicine,  
Baltimore, MD 21287; Adjunct Assistant Professor of Pediatrics, Baylor  
College of Medicine, Houston, TX 77030, USA

*Barbara R. Silverstone, JD*

Staff Attorney, National Organization of Social Security Claimants'  
Representatives, Englewood Cliffs, NJ 07632, USA

*Travis Thompson, PhD*

Executive Program Director, Minnesota Autism Center, Minneapolis,  
MN 55413, USA

*Daniel L. Van Dyke, PhD*

Co-Director, Cytogenetics Laboratory, Mayo Clinic, Rochester, MN  
55905, USA

*Robert H. Wharton, MD<sup>†</sup>*

Spalding Rehabilitation Hospital, Boston, MA 02114, USA

*Barbara Y. Whitman, PhD*

Professor of Pediatrics, Saint Louis University School of Medicine, Car-  
dinal Glennon Children's Hospital, St. Louis, MO 63104, USA

*David A. Wyatt*

Crisis Intervention Counselor, Prader-Willi Syndrome Association  
(USA), Sarasota, FL 34242, USA

*Mary K. Ziccardi, BS*

Administrator, The MENTOR Network, REM Ohio, Inc., Cleveland,  
OH 44125, USA

<sup>†</sup>Deceased.

# Part I

## Diagnosis and Genetics

# Clinical Findings and Natural History of Prader-Willi Syndrome

Merlin G. Butler, Jeanne M. Hanchett, and Travis Thompson

## Historical and Genetic Overview

Prader-Willi syndrome (PWS) is a complex genetic condition characterized by a range of mental and physical findings, with obesity being the most significant health problem. PWS is considered to be the most common genetically identified cause of life-threatening obesity in humans and affects an estimated 350,000–400,000 people worldwide. The Prader-Willi Syndrome Association (USA) is aware of more than 3,500 persons with this syndrome in the United States from an estimated pool of 17,000–22,000.<sup>37</sup> Prader-Willi syndrome has an estimated prevalence in the range of 1 in 8,000 to 1 in 20,000 individuals.<sup>17,42</sup> Although PWS is thought to be one of the more common disorders seen for genetic services, pediatricians may only encounter a few patients during their lifelong clinical practice. It is present in all races and ethnic groups but reported disproportionately more often in Caucasians.<sup>38</sup> Most cases are sporadic; however, at least 20 families have been reported in the literature with more than one affected member, including twins. The chance for recurrence is estimated to be less than 1%.<sup>43</sup> However, in some families where defective control of differentially expressed genes through errors in the process of genomic imprinting (described in detail in Chapter 3) is present in the PWS child and in the father, then the recurrence may be as high as 50% for having additional children with PWS.<sup>12,13</sup>

Prader-Willi syndrome was apparently first documented in an adolescent female by J. Langdon Down in 1887,<sup>54</sup> but it was not described in the medical literature until about 70 years later. This adolescent female had mental deficiency, obesity, short stature, and hypogonadism, and the condition was referred to as polysarcia. In 1956, Prader, Labhart, and Willi reported nine individuals (five males and four females between the ages of 5 and 23 years) with similar clinical findings.<sup>110</sup> Since the 1970s, the disorder has been referred to as the Prader-Willi syndrome.

In 1981, Ledbetter and others<sup>93</sup> first reported the cause as an interstitial deletion of the proximal long arm of chromosome 15 at region

q11–q13 in the majority of subjects studied using high resolution chromosome analysis (Figure 1.1). The syndrome became one of the first genetic syndromes to be attributed to a chromosome microdeletion detectable with new high resolution chromosome or cytogenetic methods allowing for more precision than previously available. Butler and Palmer in 1983<sup>35</sup> were the first to report that the origin of the chromosome 15 deletion was *de novo*, or due to a new event, and not present in either parent. The chromosome 15 leading to the deletion was donated from the father in all cases, as determined by studying minor normal variations (chromosome polymorphisms) in chromosome structure. This puzzling observation of finding only a paternal deletion was later clarified by molecular genetic techniques and the reporting of a maternal deletion in a separate clinical condition recognized as Angelman syndrome (AS). The molecular genetic findings will be discussed later.

The cytogenetic deletion of chromosome 15 was seen in approximately 60% of persons with PWS while the remaining subjects showed normal chromosome 15s, translocations, or other abnormalities of chromosome 15.<sup>17,32,93</sup> Butler and others in 1986<sup>32</sup> also reported clinical differences in those PWS subjects with and without the chromosome 15 deletion. Those individuals with the deletion were more homogeneous in their clinical presentation and were hypopigmented. Because of the

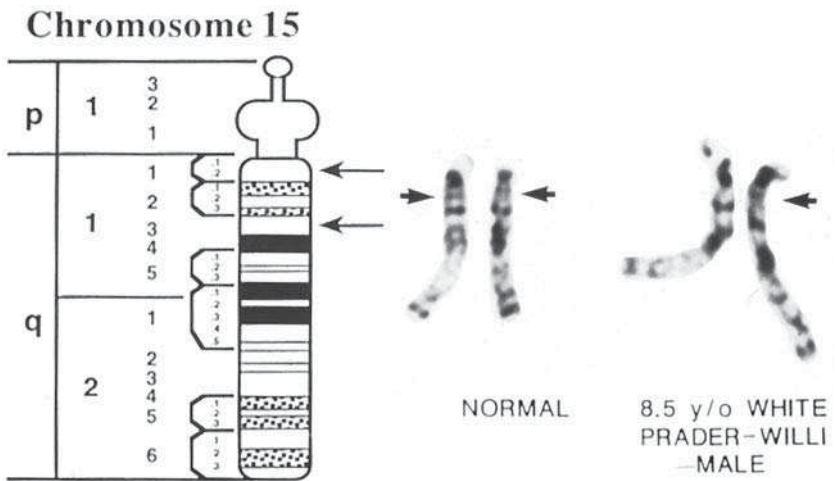


**Figure 1.1.** A prometaphase or high resolution chromosome 15 ideogram (left) showing the pattern for chromosome arms (p for short arm and q for long arm) and designated bands with two representative chromosome 15 pairs (right). The arrows on the ideogram indicate the deletion breakpoints at bands 15q11 and 15q13. The 15q12 band is indicated by the arrow on each member of the chromosome 15 pair that is normal. The left member of the chromosome 15 pair from the 8.5-year-old male with Prader-Willi syndrome shows the deletion. Modified from Butler, Meaney, and Palmer, *American Journal of Medical Genetics* 1986;23:793–809.<sup>32</sup>

hypopigmentation and other eye findings (e.g., strabismus), visual evoked potential studies of specific brain wave patterns stimulated by visual images seen by the patient were performed by Creel et al.<sup>48</sup> They reported abnormal visual evoked potentials in PWS subjects similar to what was seen in individuals with classic albinism. They further reported misrouting of the optic nerve as it crossed over at the chiasma and described that optic nerve fibers crossed over 20 degrees or more from the temporal side of the retina at the chiasma instead of projecting to the same or ipsilateral side of the brain hemisphere. This occurred more often in PWS subjects with hypopigmentation. Misrouting of the optic nerve can lead to strabismus and/or nystagmus, which are frequently seen in PWS.

Molecular genetic methods using a technique referred to as Southern hybridization of newly identified polymorphic DNA markers isolated from the 15q11–q13 chromosome region were studied by Nicholls, Butler, and others in 1989.<sup>107</sup> PWS individuals with normal-appearing chromosomes were surprisingly found to have both chromosome 15s from the mother. This finding was referred to as maternal uniparental disomy 15 (i.e., both 15s from the mother) or UPD (Figure 1.2). Studies have shown that both members of the chromosome 15 pair were inherited from the mother as a result of an error in egg production due to nondisjunction in meiosis; the chromosome 15 pair fails to separate normally when the chromosome number is reduced by one half in production of the gamete. When a single chromosome 15 is received from the father in the normal sperm then trisomy 15 results, or three chromosome 15s are present in the fertilized egg. Subsequently, loss of



**Figure 1.2.** Polymerase chain reaction amplification of genomic DNA using D15S822 locus from the 15q11–q13 region from a Prader-Willi syndrome family with normal chromosome studies in the Prader-Willi syndrome individual. The mother (on the left), the Prader-Willi syndrome individual (in the middle), and the father (on the right) each show two DNA bands representing the presence of the D15S822 locus in each chromosome 15 (nondeleted status). The DNA pattern from the mother and Prader-Willi syndrome individual are identical but no DNA signal from chromosome 15 was inherited from the father. The Prader-Willi syndrome individual has two chromosome 15s from the mother and no chromosome 15 from the father, demonstrating maternal disomy 15 or both 15s from the mother.



the father's chromosome 15 occurs in early pregnancy. This loss of a single chromosome 15 in the cells rescues the fetus. If the trisomic 15 finding had continued in each cell of the fetus, a spontaneous miscarriage would have occurred. Chromosome abnormalities, specifically trisomy 15 and other trisomy and monosomy events, are common causes of spontaneous miscarriages.

PWS and Angelman syndrome, an entirely different clinical disorder generally due to a maternal deletion of the 15q11–q13 region, were the first examples of genomic imprinting in humans, or the differential expression of genetic information depending on the parent of origin. Thus, gene activity differences exist in maternal and paternal chromosome 15s that impact on the clinical phenotype or outcome.

There are two forms of maternal disomy 15 in PWS, maternal isodisomy and maternal heterodisomy. Maternal isodisomy refers to the presence of identical genetic material (e.g., came from the same chromosome 15 in the mother during production of the egg), and maternal heterodisomy refers to the presence of genetic material from two different chromosome 15s received from the mother. Children with PWS due to maternal isodisomy may be at increased risk of having a second genetic condition if the mother is a carrier of a recessive disorder on chromosome 15 such as Bloom syndrome. Bloom syndrome is an autosomal recessive condition where the gene is located outside of the 15q11–q13 region but both members of the gene pair (alleles) are abnormal. If the mother carries an abnormal gene allele for Bloom syndrome on one of her chromosome 15s, she is unaffected because the gene allele on her other chromosome 15 is normal. However, if the chromosome 15 region or segment containing the abnormal recessive gene allele for Bloom syndrome is donated to the child by the mother in an isodisomy fashion (i.e., both chromosome 15s contain the same identical genetic information or alleles), then PWS results as well as Bloom syndrome.

PWS is thought to be due to a contiguous gene condition involving several genes, with nearly one dozen genes or transcripts mapped to the 15q11–q13 region known to be imprinted; most are paternally expressed (active) or maternally silent. Several of these genes are candidates for causing features recognized in PWS including *SNURF*/*SNRPN*, *NDN*, *snoRNAs*, *MKRN3*, and *MAGEL*.<sup>2,8,9,106</sup> The best characterized paternally expressed gene studied to date is *SNRPN* (small nuclear ribonucleoprotein N). A second DNA sequence of *SNRPN* is termed *SNURF* (*SNRPN* upstream reading frame), consisting of gene exons 1–3, which encompasses the imprinting center or the genetic locus that controls the regulation of imprinting, or turning on and off the activity of specific genes throughout the chromosome 15q11–q13 region. The proteins coded for by *SNRPN* and *SNURF* are not present in subjects with PWS. Further, chromosome translocations involving the paternal chromosome 15 that disrupt *SNURF* have been reported in subjects with typical features of PWS.<sup>37</sup> Thus, a disruption of this gene locus will cause loss of function of paternally expressed genes in this region (e.g., *MAGEL2*) and loss of proteins coded by the genes. Hence, many of these paternally expressed

genes in this chromosome area play a role in brain development and function, key for producing the clinical phenotype recognized in PWS. Detailed descriptions of the 15q11–q13 genes, their respective roles in PWS (and AS), and imprinting will be described in more detail elsewhere (see Chapter 3).

Genomic imprinting appears important for growth in humans and other mammals. Many conditions now thought to be due to genomic imprinting, such as Beckwith-Weidemann and Russell-Silver syndromes, present with either overgrowth or growth retardation.<sup>19</sup> Many imprinted genes identified to date are involved with regulation of cell proliferation or differentiation. They may also play a role in development of tumors. Some imprinted genes are known as fetal growth factors; thus, a close relationship exists between genomic imprinting and early fetal development. Generally, maternal genes have a tendency to suppress growth of the developing fetus while paternal genes enhance growth. The competition for expression of maternal and paternal genes has evolved to control growth of the fetus, and fine-tuning of expression of genes depends on the parent of origin with a complex balance of maternal and paternal genes. A disruption of the genetic balance results in growth anomalies in the fetus.

## Clinical Presentation and Diagnosis

Many clinical features in PWS may be subtle or non-specific while other features are more characteristic for the disorder. The primary features of PWS include infantile hypotonia, feeding difficulties, mental deficiency, hypogonadism, behavior problems (temper tantrums, stubbornness, obsessive-compulsive disorder), hyperphagia and early childhood onset of obesity, small hands and feet, endocrine disturbances including recently identified growth hormone deficiency, and a characteristic facial appearance (small upturned nose, narrow bifrontal diameter, dolichocephaly, down-turned corners of the mouth, sticky saliva, almond-shaped eyes, and strabismus) (Figure 1.3, see color insert). Table 1.1 lists the clinical manifestations, frequency, and time period when they occur. Some of the characteristics are subtle but well recognized by clinical geneticists trained in dysmorphology; however, a greater awareness by pediatricians, other physicians, and health care providers now exists. Because of the better recognition and awareness of PWS by the medical community during the past 10 years and more accurate and reliable genetic testing, the diagnosis is made earlier than in the past and extensive diagnostic procedures avoided. Many children with PWS were not diagnosed in the past until rapid weight gain leading to obesity was evident and the presence of specific learning/behavioral problems was observed. For example, in the mid-1980s Butler reported that the average age at diagnosis for PWS was greater than 6 years of age.

In 1993, Holm, Cassidy, Butler, and others<sup>85</sup> developed consensual diagnostic criteria to assist in the diagnosis of PWS using major and

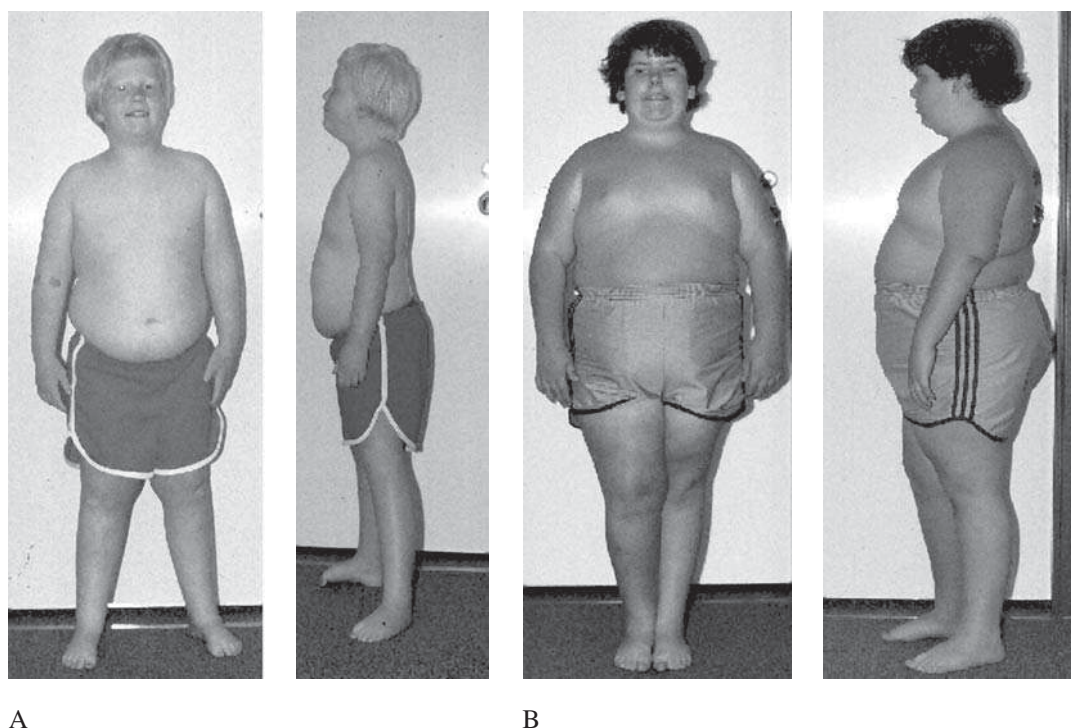


**Figure 1.3.** Frontal and profile views of two males (patient **A** is 8.5 years of age, with the chromosome 15q11–q13 deletion [seen in Figure 1.1]; patient **B** is 11 years of age, with maternal disomy 15) with Prader-Willi syndrome. Note the typical facial appearance (e.g., narrow bifrontal diameter, almond-shaped eyes, triangular mouth), small hands and feet, characteristic obesity, and hypopigmentation (seen in patient **A** with the 15q11–q13 deletion). Modified from Butler, *American Journal of Medical Genetics* 1990;35:319–332.<sup>17</sup> (See color insert.)

minor features and established a scoring system for patients presenting with features seen in this syndrome. The scoring system consisted of three categories (major, minor, and supportive criteria) and scoring was based on a point system. The major criteria were weighed at one point each while minor criteria were weighed at one half point each. Supportive criteria received no points but may be helpful to confirm the diagnosis. The diagnostic criteria for PWS and recommendations for their current use as an indicator for genetic testing are discussed in Chapter 2.

Cytogenetic studies using fluorescence *in situ* hybridization (FISH) of chromosome 15q11–q13 DNA probes became available in the 1990s and have been helpful in detecting deletions (Figure 1.4, see color insert). If the DNA probes isolated from the 15q11–q13 region do not hybridize, or attach, to this chromosome region, then the deletion status is confirmed. These studies have shown that 70% of subjects

**Table 1.1. Summary of Clinical Findings in Individuals Reported with Prader-Willi Syndrome\***

| Time period when clinical manifestations first appear | Clinical manifestation                      | Affected/total patients | Overall (%) |
|-------------------------------------------------------|---------------------------------------------|-------------------------|-------------|
| Pregnancy and delivery                                | Reduced fetal activity                      | 137/181                 | 76          |
|                                                       | Nonterm delivery                            | 83/203                  | 41          |
|                                                       | Breech presentation                         | 56/212                  | 26          |
| Neonatal and infancy                                  | Delayed milestones                          | 405/412                 | 98          |
|                                                       | Hypogenitalism/hypogonadism                 | 270/285                 | 95          |
|                                                       | Hypotonia                                   | 504/538                 | 94          |
|                                                       | Feeding problems                            | 445/479                 | 93          |
|                                                       | Cryptorchidism                              | 240/273                 | 88          |
|                                                       | Narrow bifrontal diameter                   | 138/184                 | 75          |
|                                                       | Low birth weight (<2.27 kg)                 | 68/226                  | 30          |
| Childhood                                             | Mental deficiency                           | 504/517                 | 97          |
|                                                       | Obesity                                     | 287/306                 | 94          |
|                                                       | Small hands and feet                        | 237/286                 | 83          |
|                                                       | Skin picking                                | 261/330                 | 79          |
|                                                       | Short stature (<-1 SD)                      | 232/306                 | 76          |
|                                                       | Almond-shaped eyes                          | 151/202                 | 75          |
|                                                       | Strabismus                                  | 259/494                 | 52          |
|                                                       | Delayed bone age                            | 74/148                  | 50          |
|                                                       | Scoliosis                                   | 159/360                 | 44          |
|                                                       | Personality problems                        | 161/397                 | 41          |
|                                                       | Early dental caries/enamel hypoplasia       | 56/141                  | 40          |
| Adolescence and adulthood                             | Menstruation                                | 38/98                   | 39          |
|                                                       | Reduced glucose tolerance/diabetes mellitus | 74/371                  | 20          |
|                                                       | Seizures                                    | 40/199                  | 20          |

\* Number of males 286; number of females 211.

Adapted from M. G. Butler, "Prader-Willi syndrome: current understanding of cause and diagnosis," *American Journal of Medical Genetics* 1990; 35:319-332.<sup>17</sup>

with PWS have the typical chromosome 15q11-q13 deletion (Figure 1.1) while about 25% have normal-appearing chromosomes. Currently, DNA tests of children with PWS and normal-appearing chromosomes with normal FISH studies, in comparison with parental DNA, have shown maternal disomy 15, or UPD, in the vast majority (Figure 1.2). A small percentage (1%-3%) of those PWS subjects with normal-appearing chromosomes and normal biparental chromosome 15 inheritance have either very small atypical deletions (undetectable with FISH) or mutations (defects) such as microdeletions of the imprinting center. All three genetic causes (deletion, maternal disomy, and imprinting defects) can be identified by abnormal methylation testing. Other rare genetic causes include translocations or inversions involving the chromosome 15q11-q13 region. Table 1.2 lists the genetic testing available to identify the genetic cause in PWS subjects. Molecular and cytogenetic testing for this syndrome will be described in more detail elsewhere (see Chapter 4).



**Figure 1.4.** Representative fluorescence *in situ* hybridization (FISH) using a SNRPN probe from the chromosome 15q11-q13 region (red color), a centromeric probe from chromosome 15 (green color), and a distal control probe from chromosome 15q (red color) showing the absence of the SNRPN signal close to the centromere on the deleted chromosome 15 from a subject with Prader-Willi syndrome. (See color insert.)

| Table 1.2. Genetic Laboratory Testing for Prader-Willi Syndrome                                                                                                                                                                                                                                                            |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 1. Chromosome analysis to rule out translocations                                                                                                                                                                                                                                                                          |
| 2. Fluorescence <i>in situ</i> hybridization (FISH) analysis using DNA probes from chromosome 15q11-q13                                                                                                                                                                                                                    |
| 3. DNA methylation testing of SNRPN gene with polymerase chain reaction (PCR)                                                                                                                                                                                                                                              |
| 4. DNA microsatellite analysis using PCR to confirm a paternal 15q11-q13 deletion and size (type I or type II) in PWS or to identify maternal disomy 15; DNA from the patient and each parent will be required.                                                                                                            |
| 5. Gene expression studies of imprinted genes (e.g., paternally expressed [maternally silent] SNRPN gene) from the 15q11-q13 region using reverse transcriptase-PCR. The lack of paternally expressed genes will confirm the diagnosis of PWS but will not assign the genetic subtype (e.g., deletion or maternal disomy). |
| 6. DNA replication pattern analysis of genes from the 15q11-q13 region varies depending on the parental source of chromosome 15.                                                                                                                                                                                           |
| Tests 1, 2, and 3 are usually performed in subjects presenting to the genetics clinic with features of PWS, while tests 4, 5, and 6 are research-based tests and available in research laboratories only.                                                                                                                  |



## Clinical Stages and Natural History

The course and early natural history of PWS can be divided into two distinct clinical stages. The first stage occurs during the neonatal and early infancy periods and is characterized by varying degrees of hypotonia, a weak cry, a narrow forehead, developmental delay, temperature instability, a poor suck reflex, sticky saliva, feeding difficulties sometimes requiring gastrostomy or stomach tube placement, hypogonadism, and underdevelopment of the sex organs. Failure-to-thrive is noted during this first stage. The hypotonia is thought to be central in origin, non-progressive, and on the average begins to improve between 8 and 11 months of age.<sup>32</sup> Infants with PWS sit independently at 11–12 months, crawl at 15–16 months, walk at 24–27 months, and talk (10 words) at 38–39 months.<sup>32,72</sup> The delay in achieving motor milestones appears to relate more to psychomotor development than to excessive obesity. Language appears to be the most delayed of the developmental milestones.<sup>32,72</sup>

The second stage usually begins around 2 years of age and is characterized by continued developmental delay or psychomotor retardation and onset of hyperphagia leading to obesity. Other features noted during the second stage may include speech articulation problems, foraging for food, rumination, unmotivated sleepiness (found in greater than 50% of subjects), physical inactivity, decreased pain sensitivity, skin picking and other forms of self-injurious behavior, prolonged periods of hypothermia, strabismus, hypopigmentation, scoliosis, obstructive sleep apnea, and abnormal oral pathology (enamel hypoplasia, dental caries, malocclusion, and decreased saliva).<sup>37</sup>

Early in the second stage, infants and toddlers are usually easy-going and affectionate, but in about one half of PWS subjects personality problems develop between 3 and 5 years of age. Temper tantrums, depression, stubbornness, obsessive compulsivity, and sudden acts of violence of varying degrees may be observed during this stage. These behavioral changes may be initiated by withholding of food but may occur with little provocation during adolescence or young adulthood. Poor peer interactions, immaturity, and inappropriate social behavior may also occur during this time.<sup>17,57,58,61,127</sup>

### Pregnancy and Delivery

Decreased fetal movement is noted by the mothers in nearly all PWS pregnancies. About one fourth of babies with PWS are delivered in breech presentation. Approximately one half of babies with PWS are born pre- or post-term (2 weeks earlier or later than the anticipated delivery date). Mild prenatal growth retardation is noted, with an average birth weight of 2.8 kg. Low birth weight is seen in about 30% of deliveries.<sup>17</sup>

### Infancy

Because of generalized hypotonia, neonates with PWS are profoundly floppy and their presentation can be mistaken for other disorders such as Werdnig-Hoffman or trisomy 18 syndromes, a brain anomaly or

bleeding, a metabolic disturbance, an infectious agent, or other environmental insult. The hypotonia may lead to asphyxia and, in the past, has led to extensive medical evaluations including muscle biopsies and repeated brain imaging studies. Most of the structural brain imaging studies and muscle biopsies performed on infants are thought to be normal or not diagnostic for a specific syndrome.

Most infants with PWS have a weak or absent cry, little spontaneous movement, hyporeflexia, excessive sleepiness, and poor feeding due to diminished swallowing and sucking reflexes that may necessitate gavage feedings lasting for several months. However, feeding difficulties generally improve by 6 months of age. Failure-to-thrive and poor weight gain are common features seen in infants with PWS. Due to failure-to-thrive, feeding difficulties, and hormone deficiencies, the growth of the PWS infant may fall below the 3rd centile for weight. Temperature instability may be present during early infancy with high or low body temperatures. The bouts of hyperthermia or fever may trigger medical investigations to pursue an infectious agent, which is not often found. Infants with PWS have significant respiratory abnormalities including sleep-related central and obstructive apneas and reduced response to changes in oxygen and carbon dioxide levels.<sup>4,108,136</sup> PWS subjects tend to be relatively insensitive to pain including that caused by obtaining blood samples. Cryptorchidism (undescended testicles) and a hypoplastic penis and scrotum are frequently seen in males and hypogonitalism in females. Cryptorchidism may require treatment (hormonal and/or surgery), and a referral to a pediatric urologist is warranted (see Chapter 5). In addition, the hands and feet may be small at birth.

Mild dysmorphic features are recognized during the infancy period, particularly involving the face. These features include a narrow forehead; mild upward slanting of the palpebral fissures; a long, narrow-appearing head (dolichocephaly); a small upturned nose; a thin upper lip; sticky saliva; and down-turned corners of the mouth. Many of the dysmorphic facial features are reminiscent of those due to midline central nervous system defects, while others such as a triangular mouth may be related to hypotonia and poor prenatal neuromuscular functioning. PWS subjects may have diminished facial mimic activity due to the muscular hypotonia as they grow older. They may also present with hypopigmentation for their family background, including fair skin and light hair color noted during the infancy period. Hypopigmentation relative to family background is a feature in about three fourths of PWS subjects and correlates with those individuals having the 15q11–q13 deletion and loss of the *P* gene (which causes oculocutaneous albinism type II) located in this region.<sup>16</sup>

As noted above, infants with PWS tend to sit at 11–12 months and crawl at 15–16 months on average. Developmental milestones are typically delayed, and the delay continues into childhood.

### Early Childhood

Although infants with PWS may be tube-fed during infancy, by 18 months to 2 years of age their feeding behavior changes radically and

an insatiable appetite may develop, which causes major somatic and psychological changes in early childhood. Along with global developmental delays, temper tantrums, difficulty in changing routines, stubbornness, controlling or manipulative behavior, and obsessive-compulsive behavior may become more apparent during childhood. Lying, stealing, and aggressive behavior are common during the childhood years and may continue into adolescence and adulthood. Children with PWS may be less agreeable, less open to new ideas and experiences, and more dependent than typically developing children. In addition, they are generally less physically active than other children their age. Frequently, medical and/or behavior management advice is sought to treat the behavioral problems. Medications such as serotonin reuptake inhibitors have been of benefit in controlling behavior and psychiatric disturbances in some children with PWS, particularly as they become older.<sup>42,43</sup>

On average, toddlers with PWS learn to walk at about 27 months of age. By the time they enter kindergarten, they are nearly always overweight and short for age. However, growth hormone treatment significantly improves body composition, stature, and energy level. PWS children should be evaluated and treated for endocrine abnormalities such as hypothyroidism and growth retardation. In addition, enamel hypoplasia and dental caries are frequently seen during childhood in the syndrome. During early childhood PWS children may also develop nystagmus or strabismus, but the most common recognized eye finding in PWS is myopia,<sup>64</sup> followed by decreased visual acuity and impaired stereoscopic vision; the latter finding is more common in PWS subjects with maternal disomy 15.<sup>65</sup> The hypopigmentation becomes more pronounced during childhood, particularly in those PWS subjects with the 15q11–q13 deletion.

The small hands and feet may not be apparent at birth but become more recognized during mid-childhood. Almond-shaped eyes may be more noticeable during childhood due to the periorbital tissue shape. A characteristic body habitus or posture, including sloping shoulders, heavy mid-section, and *genu valgus* with straight lower leg borders and sparing of distal extremities from excess fat deposition, is usually present by toddlerhood.

About one third of children with PWS function in the low-normal intellectual range (70–100 IQ), and the remaining PWS children (and adults) function in the mild-to-moderate range of mental retardation (50–70 IQ).<sup>37,125</sup> The average IQ is 65, with a range of 20 to 100. Academic achievement is poor for cognitive ability. During the first 6 years of life, children with PWS often do not achieve normal levels of cognition, motor, or language development. There are reported differences in behavior, academic, and intelligence testing between the PWS subjects with the typical chromosome 15 deletion versus those with maternal disomy, which will be discussed later in this chapter (see also Chapter 8).

Many children with PWS begin school in mainstream settings. About 5% attend regular school until secondary level, but the intellectual impairment and potential behavioral problems present in the majority



of children with the syndrome require special education and support services. By elementary school age, children with PWS may steal or hide food at home or during school to be eaten later. It is common for those with PWS to have relatively strong reading, visual, spatial, and long-term memory skills but relatively weak math, sequential processing, and short-term memory skills. Verbal skills are relative strengths, particularly in those PWS subjects with maternal disomy, although speech articulation is often poor, with nasal or slurred characteristics. An unusual skill with jigsaw puzzles and fine motor skills are particularly common in those with the typical 15q11–q13 deletion. Recent studies have documented genotype/phenotype differences between the two genetic subtypes (deletion vs. maternal disomy), which may impact on these skills. Additional psychobehavioral findings in children with PWS will be discussed in more depth elsewhere (see Chapters 8 and 12).

### **Adolescence and Adulthood**

Normal puberty is absent or delayed in both males and females with PWS. Gonadotropin hormone production by the brain is low, and other endocrine disturbances may be identified in this subject population. As a result, adolescents and young adults with PWS look young for their chronologic age. The occurrence of reduced growth hormone secretion and hypogonadotropic hypogonadism in the majority of children and adolescents with PWS, along with an insatiable appetite and high pain threshold, would suggest a hypothalamic pituitary dysfunction.

Hypogonadism and hypogenitalism occur in the vast majority of males and females with PWS and become more evident during adolescence. The hypogonadism is due to hypothalamic hypogonadotropism, since it is often associated with low levels of gonadotropin released by the brain needed for gonadal development and function. The degree of hypogonadism is variable from patient to patient but more marked in males. Cryptorchidism occurs with a hypoplastic penis and scrotum in males and can be identified in early infancy, but the hypoplastic labia minora and clitoris in females may not be as easily recognized, although they are cardinal features of this syndrome. Sertoli cells and a variable number of Leydig and germinal cells are usually present in the testicles, although there have been no reports of fertility in males. In addition, the tubules are usually small and atrophic. Penile size increases modestly in many males during the third or fourth decade of life, but testicular size remains small. In males with palpable testes, the size is seldom greater than 6 ml in volume. Treatment of the small penis with topical or parenteral testosterone has been effective in achieving penile growth in PWS males.<sup>40</sup> However, mature genital development in males is rarely seen. Gonadotropin treatment may also be helpful in treating PWS males with cryptorchidism. Cryptorchid testes may descend spontaneously in some patients during childhood and puberty, but surgical intervention may be indicated. Precocious development of pubic and axillary hair occurs frequently as a consequence of premature adrenarche. Beard and body hair are variable, occurring later than

normal, if at all. Beard growth is absent in about 50% of men.<sup>45</sup> Additional endocrine-related findings and more in-depth discussions are presented in later chapters (see Part II).

Menarche is often late or does not occur in females with PWS. In 98 appropriately aged females reported in the literature,<sup>17</sup> 38 developed spontaneous menstruation (see Table 1.1). In a study of mostly adult PWS females, breast development was normal in about one half, with onset between 9 and 13 years of age.<sup>72</sup> Primary amenorrhea (absence of menstruation) was found in about 70% of females and oligomenorrhea (infrequent menstruation) in the remaining. Age of menarche is extremely wide, from 7.5 to 38 years. In a series of 106 females between the ages of 15 and 63, 13 had been given hormones to induce menses. Very few of the women who had spontaneous menarche had regular menses; most had scant and infrequent menses.<sup>76</sup> Pubic hair was normal in 40% of females studied.<sup>72</sup>

Two women with presumed PWS were reported in the 1970s with established pregnancies (one woman was pregnant on two separate occasions).<sup>92</sup> However, the diagnosis of PWS was not confirmed with genetic testing in the two reported females. More recently, at least two women with documented PWS, confirmed by cytogenetic and molecular genetic methods, have been reported with established pregnancies. One woman with PWS was 33 years of age and had suspected maternal disomy (i.e., abnormal methylation testing and normal chromosome study with FISH). She gave birth to a healthy girl by C-section delivery after an estimated 41 weeks gestation.<sup>2</sup> The other adult female had the 15q deletion and gave birth, not surprisingly, to an infant with Angelman syndrome due to the child's receiving the 15q deletion from its mother.<sup>116</sup> The mother with PWS and suspected maternal disomy had low cerebrospinal fluid concentration of 5-hydroxyindoleacetic acid, a serotonin metabolite.<sup>2</sup> Due to behavioral problems before pregnancy, she had been medically treated with serotonergic drugs, which may have influenced gonadotropin release to induce hormonal conditions required for pregnancy and possibly reflecting low serotonin synaptic transmission in the brain. Warnock et al.<sup>133</sup> also reported onset of menses in two adult females with PWS when treated with fluoxetine, a serotonin reuptake inhibitor that increases the available serotonin for brain function. Therefore, fertility in women with PWS is exceedingly rare, but reproductive issues should be addressed in reproductive-age females with PWS.

Approximately 90% of subjects with PWS without growth hormone treatment will have short stature by adulthood. The average adult male without growth hormone therapy is 155 cm (61 inches) tall, and the adult female averages 147 cm (58 inches).<sup>31</sup> Growth standards for Caucasian PWS males and females aged 2 to 22 years, without a history of growth hormone therapy, were reported by Butler and Meaney in 1991<sup>31</sup> and are used in the clinical setting in the United States to monitor growth parameters (see Appendix C). These growth standards illustrate the growth pattern anomalies in this syndrome compared with healthy subjects. For example, the 50th centile for height in the PWS group fell below the normal 5th centile by the age of 12 to 14 years,

while the 50th centile for weight in the PWS group approximated the 95th centile in the healthy control group. Height may follow the 10th centile or below until the age of 10 years for females and 12 years for males, at which time the height velocity often declines relative to normal due to the lack of a growth spurt. Growth standards for PWS from other countries have also been reported (see Appendix C). Growth hormone therapy may increase the growth spurt and impact positively on the ultimate height and body composition in the PWS subject (see Chapter 7).

Inverse correlations have been reported with linear measurements (e.g., height, hand and foot lengths) and age, indicating a deceleration of linear growth with increasing age relative to normal individuals.<sup>30</sup> A relative deceleration in growth of certain craniofacial dimensions (e.g., head circumference, head length) was also suggested.<sup>98</sup> Therefore, dolichocephaly or a long, narrow head shape may be considered an early diagnostic sign for PWS.

Small hands with thin, tapering fingers and small feet (acromicria) are seen during infancy and childhood and become more pronounced during adolescence and adulthood. There is a straight ulnar border of the hands. Foot length tends to be more affected than hand length, compared with normative standards. The average adult shoe size for males not treated with growth hormone is size 5 and for females size 3. Therefore, short stature and small hands and feet are present in the majority of PWS subjects, although the frequency in blacks is lower.<sup>86</sup> There is relative sparing of the hands and feet from obesity, with fat distribution often appearing to end abruptly at the ankle and wrist. Scoliosis may also become more pronounced during the adolescent period, and kyphosis may be present by early adulthood.

Without intervention, adolescents with PWS may weigh 250 to 300 pounds by their late teens, which can lead to a shortened life from the complications of obesity. Overeating can lead to immediately life-threatening events such as stomach rupturing. By late adolescence, some with PWS begin stealing food from stores and rummaging through discarded lunch bags or trash cans to find partially eaten left-over food or inedible food items (e.g., bags of sugar, frozen food). Some parents find it necessary to lock the refrigerator and cabinets containing food to prevent excessive eating. Despite these precautions, youth with PWS may pry open locked cabinets to gain access to food. In the past, many patients with PWS died before the age of 30 years. The eating behavior, complications of obesity that can reduce the life expectancy of a person with PWS, and cognitive impairments will preclude normal adult independent living. Behavioral and psychiatric problems interfere with quality of life in adulthood and may require medical treatment and behavioral management. However, if weight is adequately controlled, life expectancy may be normal. Hence, caloric diet restriction is lifelong and important to control the obesity and its complications. Continued consultation with a dietitian with experience in Prader-Willi syndrome is recommended.

Adults with PWS have generalized mild hypotonia and decreased muscle bulk and tone, poor coordination, and often decreased muscle

strength. However, muscle electrophysiological and biopsy studies are generally normal or non-specific. The decreased muscle tone and muscle mass contribute to the lower metabolic rate, leading to physical inactivity and obesity, although thyroid function tests have generally been within normal range but not adequately studied to date.<sup>17</sup>

Sleep disorders and respiratory dysfunction such as hypoventilation and oxygen desaturation are common from childhood to adulthood for the PWS subject. Adolescents with PWS have a tendency to fall asleep during the day, particularly when they are inactive. They do not sleep soundly and may awaken often during the night; some may forage for food.

Behavioral and learning problems may become more prominent during the teenage years, particularly temper tantrums and obsessions. Typical adolescent rebelliousness is often exaggerated in those with PWS, particularly over access to food. Psychotropic agents can be helpful in controlling abnormal behavior, but no specific medication has been universally effective in controlling abnormal behavior or food-seeking behavior. The use of medication to control behavior problems will be discussed in more detail elsewhere (see Chapter 12). It should be noted that children and adults with PWS are typically affectionate and outgoing, like to please others, and seek positive attention.

Typical behavior problems include rigidity of personality, perseveration in conversation, tantrums, obsessive-compulsive symptoms, and noncompliance. Occasionally these worsen during adulthood. In some adults, symptoms of psychosis can be seen. Acute psychosis can be seen in young adulthood in about 10% of PWS patients. Recently, individuals with maternal disomy were reported to have a higher risk of developing psychoses during adulthood.<sup>132</sup> Detailed genotype/phenotype correlations addressing these and other issues will be discussed elsewhere.

When an adult with PWS is surrounded by caregivers who have been trained in the management of PWS, behaviors can be managed. Many persons can become happy members of their community. When the environment is one in which caregivers are not aware of the specific needs of adults with PWS, behavioral deterioration can be expected.

The adult with PWS may have goals for himself or herself similar to those of any other person entering adulthood: establishing vocational goals, deciding where to live, and desiring to become independent in decision-making. This sometimes leads to conflict and frequently causes an exacerbation of health and behavior problems. For most persons with PWS, formal education ends between ages 18 and 21. If vocational training has been successfully introduced before then, a smooth transition to the world can occur. Unfortunately, many individuals do not have this available to them and a gap exists between completion of school and entrance into a job-training program. This loss of daytime structured activities usually results in behavioral deterioration, and health problems may occur or increase. The challenge to family members and caregivers is establishing an appropriate environ-

ment for the adult, which includes a supervised living arrangement (with food restrictions), a vocational setting appropriate for the skills and behavior of the young adult, and professional sources knowledgeable about PWS. As in childhood, limiting access to food is essential, as is skill in management of typical behavior problems. If this does not happen, deterioration in health occurs.

Assignment of legal guardianship to another adult is frequently helpful and necessary to assure a safe environment for adults with PWS. Decisions regarding living arrangements and availability of food are usually made unwisely by persons with the syndrome, and therefore it is in the best interest of the person to have guardianship legally assigned to a parent or other adult.

Some persons with PWS live into their seventh decade of life. A person who died at age 71 years was described in 1994,<sup>39</sup> and a second individual at 68 years of age was described in 2000.<sup>18</sup> Undoubtedly, there are other older persons with this syndrome who have not been reported in the literature. A review of causes of death in persons with PWS in 1996 indicated that obesity-hypoventilation syndrome caused the majority of deaths. This review included the experience of seven physicians who cared for 665 persons with the syndrome.<sup>77</sup> Twenty-five deaths had occurred, 14 of them related to obesity complications and the remainder due to several other causes. The average age at death was 23 years. The syndrome does not include any specific internal organ abnormality; therefore, if obesity is controlled and overeating avoided, life expectancy should be similar to that of other individuals with mild mental deficiencies.

## Obesity and Related Problems

Children with PWS become overweight by 2 to 4 years of age, without appropriate intervention, as a consequence of overeating due to an insatiable appetite and compulsive behavior related to food. Weight gain worsens over time due to the fact that individuals with PWS require fewer calories (40% to 70% reduction compared with non-obese controls), and it can become life-threatening if not controlled. About one third of subjects with PWS weigh more than 200% of their ideal body weight,<sup>99-101,115</sup> and without intervention significant morbidity and mortality may occur from the complications of obesity such as cardiopulmonary compromise.

Specific obesity-related findings may be seen in PWS subjects including heart failure, hypertension, thrombophlebitis and chronic leg edema, orthopedic problems, abnormal lipid profiles, and Type 2 diabetes mellitus. Premature development of atherosclerosis with severe coronary artery disease has been reported in PWS subjects.<sup>91</sup> Complications of obesity include skin rashes (particularly in fat folds), ulcers of the skin (most commonly in the lower legs), and cellulitis (particularly in lower extremities). Other obesity-related problems may include obstructive sleep apnea and narrowing of the airway, pathologic fractures, reduced physical activity, impaired respiratory function and

hypoventilation, high carbon dioxide levels, specific endocrine disturbances, risks from general anesthesia, and hypometabolism.

The primary health issues in PWS are exacerbated by obesity and related findings. When weight is kept under control, there are few serious health issues. If the weight increases, diseases associated with obesity may appear. For example, Type 2 diabetes mellitus is seen in 25% to 30% of PWS adults who become morbidly obese.<sup>15</sup> Diabetes is difficult to control with medication if food restriction is inadequate. When food intake is reduced to the appropriate number of calories, diabetes usually comes under control quickly. Symptoms of the disease disappear in most cases and blood sugar values become more normal. If this cannot be achieved, complications of diabetes may occur in a few years after the diabetes is detected. These complications may include retinopathy, neuropathy, kidney failure, and amputations. However, insulin resistance is lower in PWS subjects and insulin sensitivity is higher compared with obese individuals without PWS.<sup>123</sup>

Morbid obesity often causes obesity-related hypoventilation, which can be a serious problem and demands attention. Loud snoring, inability to sleep flat in bed, and shortness of breath with minimal exertion become noticeable. Hypoventilation and sleep apnea can reduce the oxygen level in the blood, necessitating pulmonary devices to increase oxygenation during sleep. If this is not reversed, right-sided heart failure (cor pulmonale) may ensue. Rapid weight gain, swelling of the ankles, marked shortness of breath, cyanosis, and decreased activity are signs of cardiac decompensation. Although rapid weight loss and a program of physical exercise can reverse this cascade of events, hospitalization usually becomes necessary (see Chapter 17). A reevaluation of the living environment is essential when this occurs.

### **Appetite Disorder**

As previously stated, obesity is due to several factors such as hyperphagia, a lower metabolic rate, persistent hunger, decreased perception of satiety, and an uncontrollable appetite with impaired emesis.<sup>17,40,84</sup> The intense preoccupation with food, food craving, lack of satiation, and incessant food seeking in PWS are the most striking features of the syndrome. There are clinical reports of individuals with PWS engaging in pica and eating unpalatable food items (e.g., frozen food), although people with PWS generally prefer the same foods as most other people, primarily sweet carbohydrates. It is also clear that they are willing to consume unpalatable items and even engage in pica when food access is sufficiently restricted.

We have previously demonstrated that people with PWS have elevated plasma gamma aminobutyric acid (GABA) levels,<sup>60</sup> possibly up-regulated following the loss of GABA receptor subunit genes from the chromosome 15q11–q13 region, with resulting GABA-A receptor dysfunction. GABA acts as a major brain neurotransmitter involved with inhibition. GABA-ergic compounds generally cause disinhibition, leading to even less impulse control.<sup>6</sup> People with PWS should have



little impulse control when faced with availability of food, which is commonly claimed by parents and clinicians.

Only recently have studies investigated neuropeptide or endocrine factors contributing to eating behavior.<sup>50</sup> For example, leptin produced by adipose tissue and cholecystokinin produced by the gut are mediators of satiety and eating behavior. However, no significant differences were found in fasting plasma levels for either leptin or cholecystokinin in PWS subjects compared with obese controls.<sup>23,33,109</sup> In addition, no significant differences in plasma levels were found in the two PWS genetic subtypes (typical deletion and maternal disomy). It appears that leptin levels in PWS follow the pattern observed in the normal population and are positively correlated with fat mass. Recently, ghrelin, an endogenous ligand or protein that attaches to the growth hormone secretagogue receptor (a hypothalamic G-protein-coupled receptor) produced by enteroendocrine cells of the stomach, has been found to be involved in energy balance and appetite stimulation. Adults and children with PWS were recently reported to have fasting plasma ghrelin levels three to five times higher than in non-PWS obese or non-obese subjects.<sup>50,78</sup> Infants with PWS as early as 3 months of age also have elevated ghrelin levels.<sup>21</sup> Genes from ghrelin and its receptors are also expressed in different regions of the brain in PWS and control subjects.<sup>124</sup> These observations need confirmation and additional testing before we know their role in hyperphagia and the insatiable appetite seen as cardinal features in PWS.

### Metabolism and Energy Expenditure

The morbid obesity associated with PWS is the result of chronic imbalance between energy intake and energy expenditure. It is challenging to objectively measure these two components of energy balance in PWS due to the mental and physical status of these patients, but this is essential to determine the energy expenditure per subject and specific treatment options. Preliminary studies in PWS have attempted to measure energy expenditure. For example, daily energy expenditure was reported to be 47% lower in PWS subjects compared with controls, but this difference was reduced to 14% when allowances were made for differences in fat-free mass. Basal or resting energy expenditure, corrected for fat-free mass, was similar in PWS patients compared with obese controls, suggesting that the low daily energy expenditure in PWS was mainly a result of a reduced fat-free mass (muscle) and possibly a lower level of physical activity. However, electromyograms, motor nerve conduction velocity tests, serum creatine phosphokinase, and results of light microscopy studies of muscles are usually normal in PWS,<sup>84</sup> while specialized histochemistry studies of muscles demonstrate type II muscle fiber atrophy consistent with disuse.<sup>1</sup>

Few metabolic studies are known to explain the obesity in PWS, particularly relating to adipose tissue metabolism. Thyroid hormone, lipid profiles, glucocorticoid, and amino acid levels in PWS are comparable to those in obese individuals without PWS, although reduced glucose tolerance is reported in one fifth of patients with PWS.<sup>11,34,36,75</sup>



In six PWS patients no abnormalities in fat metabolism or transport were identified in response to norepinephrine, insulin, and glucose.<sup>7</sup> While fat cells were found to be larger than in control individuals, uptake of fat and fatty acid composition in adipose tissue was normal and the fat cell number was not increased.<sup>7,69,74</sup> Levels of adipose tissue lipoprotein lipase, an enzyme that regulates uptake and storage of triglycerides, were increased 10-fold in fat biopsy specimens from seven PWS subjects compared with those of control individuals, when adjusted for percent ideal body weight and fat cell size.<sup>117</sup> This enzyme may be elevated in PWS, but additional research is needed.

Serum cholesterol and triglyceride levels are generally thought to be normal in PWS, but fat biopsy specimens reported from nine subjects with PWS showed that triglycerides make up more than 98% of the fat.<sup>105</sup> There was a demonstrated threefold increase in long-chain polyunsaturated fatty acids, which suggested a resistance to lipolysis or breakdown of fat. In addition, body composition and substrate utilization studies in 11 PWS subjects showed a higher percentage of adipose tissue, but an apparent normal substrate utilization was found with a normal percentage of fat used for basal metabolism when compared with other obese control individuals.<sup>105</sup> The roles of the elevated long-chain fatty acids and increased levels of adipose tissue lipase in the development of obesity in PWS suggested from fat biopsy specimens are not understood. In addition, the relationship, if any, to the genetic alterations of chromosome 15 is unclear.

Muscle is metabolically active tissue, while adipose or fat stores energy. Therefore, the low muscle mass in PWS significantly contributes to hypotonia, reduced physical activity, and low energy expenditure. These factors lead to storage of energy in the form of excess adipose tissue. In one study, PWS subjects expended approximately 50% less energy than healthy obese controls. Daily energy expenditure can be measured using a whole-room calorimeter to record oxygen utilization and carbon dioxide production to determine the metabolic rate and energy expenditure. Lower levels were found in PWS subjects compared with obese controls. However, no information was recorded for differences in fat-free mass or muscle.<sup>37</sup>

Hill, Butler, and others<sup>83</sup> reported resting metabolic rates in lean, obese, and PWS subjects using indirect calorimetry following an overnight fast. The PWS subjects had the lowest resting metabolic rate, followed by lean then obese subjects. The usual strong relationship observed between resting energy expenditure and fat-free mass was not found in the children studied, compared with non-PWS lean and obese controls. The study further suggested that the initial low rates of energy expenditure in subjects with PWS was independent of fat-free mass, but once patients gained a large amount of weight, the relationship appeared to normalize. Recently, Goldstone et al.<sup>70</sup> reported on 13 women with PWS, aged 20 to 38 years, and 45 control women, aged 18 to 56 years, and found differences in resting metabolic rate. Such differences could be explained by the abnormal body composition in PWS, suggesting that energy expenditure is normal at the tissue level in this syndrome.

Reduced physical activity described in PWS subjects was suggested by Schoeller et al.<sup>115</sup> as a major cause of the decreased energy expenditure requirements. Although subjects with PWS have hypotonia during infancy, which lessens during the first 1 to 2 years of life, a residual amount remains throughout life. This low muscle tone and lack of coordination may favor a sedentary lifestyle. However, few studies have attempted to quantify the levels of physical activity in PWS either in a free setting or in a controlled institutional care setting. It is thought that children with PWS are less physically active during play compared with normal children. To assess physical activity, Nardella et al.<sup>104</sup> studied children with PWS and controls attending a summer camp over a 2-week period by using portable activity meters and pedometers. They reported a wide range of activity levels in subjects with PWS compared with normal children. These results were inconclusive and furthermore did not address the situation in a free setting.

The role of altered energy expenditure and decreased metabolic rate as the causation of obesity, along with excessive caloric intake, decreased energy expenditure, and reduced physical activity leading to morbid obesity in PWS subjects, will require additional research. Growth hormone deficiency and its therapeutic use to stimulate growth, particularly to increase stature and muscle mass while decreasing fat mass and improving pulmonary function in PWS subjects, will require further long-term studies, but significant benefits have been reported. Growth hormone therapy and related endocrine and metabolic issues will be described elsewhere (see Chapter 7).

### Onset and Measurement of Obesity

The onset of obesity occurs between ages 1 and 6 years, depending on the definition of obesity, with an average age of onset by 2 years in PWS subjects without growth hormone treatment. This onset follows a period of failure-to-thrive, feeding difficulties, and hypotonia during the neonatal and early infancy period, which is designated as the first stage of PWS. The abnormal feeding noted during infancy may be due to central nervous system or brain dysfunction, particularly an abnormality of the hypothalamus, although gross neuropathologic studies have not identified a consistent brain lesion in this area. However, limited brain imaging studies with positron emission tomography for evaluating brain metabolism have indicated decreased glucose metabolism in the parietal lobes of the brain and hypothalamus in at least one adult with PWS.<sup>29</sup> In addition, recent studies have shown abnormal oxytocin levels in brains of PWS subjects<sup>97</sup> and high plasma levels of GABA,<sup>60</sup> which will require further testing.

Skinfold measurements of PWS infants do show excessive fat at an early age (6 months) and before the infant is judged to be obese by weight/height parameters.<sup>22</sup> The subcutaneous fat pattern is characteristically centrally located over the buttocks, trunk, and thighs but spares the distal regions of the extremities with the use of skinfold measurements.<sup>40,99,100,115</sup> A two- to threefold increased fat mass compared with the general population has been reported, using skinfold measurements to determine percent body fat.<sup>100</sup> This patterning has been sub-

stantiated using more current and accurate measures of obesity such as dual-energy X-ray absorptiometry (DXA); for example, 40% to 60% body fat was found using DXA in a recent study, which is about two- to threefold higher than in the general population.<sup>26</sup> There are several methods in use to determine body composition, particularly fat, such as bioelectrical impedance, which measures fat-free mass and fat mass; skinfold thickness, which measures subcutaneous fat mass at various sites; magnetic resonance imaging (MRI) of lean and fat tissues; and DXA (or DEXA), which provides a measure of fat tissue, lean tissue, and bone density. Of the methods listed, DXA is considered the most accurate in determining body composition in PWS or in healthy subjects. A thorough discussion of body composition measurement options is included later in this volume (see Chapter 6).

The fatness pattern appears to be sex-reversed, with males having more fat than females.<sup>99,100</sup> Historically, individuals with PWS were described as morbidly obese with body mass index (BMI, defined as weight in kilograms divided by height in meters squared in adults) reported<sup>11</sup> as high as  $47 \pm 4.2$ , compared with a normal BMI range between 21 and 27. There is a tendency for internal or visceral fat areas, as determined by MRI studies, to be lower in PWS subjects compared with obese subjects, as reported by Goldstone et al.<sup>71</sup> Goldstone et al. studied 13 adult females with PWS and 14 obese control women and found significantly reduced visceral fatness or adiposity in the PWS females, which is independent of their total adiposity or use of exogenous sex steroid treatment. This was in contrast to that expected by their physical inactivity, hypogonadism, growth hormone deficiency, and psychiatric problems. However, Talebizadeh and Butler<sup>123</sup> observed an overall trend for decreased visceral fat area but not significantly different in the PWS subjects compared with controls. They observed that PWS subjects with higher visceral fat area may be at an increased risk for obesity-related complications, compared with PWS subjects without an elevated visceral fat area.

The cause of the reduced visceral adiposity in PWS may reflect hormone imbalance, hypothalamic dysfunction, or genetic influence on body fat distribution. The visceral fat is positively correlated with glucose and triglyceride levels in both PWS and obese subjects and contributes to insulin resistance. A different peripheral-visceral fat storage pattern seen in PWS subjects compared with obese controls may account for the abnormal fat storage and lipolysis in PWS. In addition, insulin levels are generally lower in PWS subjects compared with obese individuals.

## Weight Management

Weight control through diet restriction, exercise programs, and/or hormone replacement is a constant key management issue throughout the life span of an individual with PWS. Diet is historically the cornerstone for controlling the obesity seen in PWS. Caloric restriction of 6–8 calories/cm of height will be required to allow for weight loss, while 10–12 calories/cm of height usually maintains weight in children with PWS, particularly in those not undergoing growth hormone therapy.

Historically, the calorie requirement to maintain weight is about 60% of normal. A low-calorie, well-balanced diet of 1,000–1,200kcal/day combined with regular exercise would be advised, but this is difficult to implement in children and adults with PWS due to the insatiable appetite and food-seeking behavior. Supplemental vitamins and calcium are recommended. Unfortunately, no medications or surgical procedures have had long-term effectiveness in controlling appetite and obesity in PWS. An exercise regime should also contribute to weight loss and may improve hypotonia, respiratory problems, and excessive daytime sleepiness and apnea common in PWS subjects. In addition, locking refrigerators and food cupboards may be required to prevent the person with PWS from obtaining additional food and from eating inappropriately. With the increasing use of growth hormone therapy in the pediatric PWS population, weight, stature, and caloric intake require close supervision by a multidisciplinary team.

Surgical procedures such as gastroplasty (reducing the size of the stomach) and intestinal bypass to correct or prevent obesity have met with only limited success in PWS (see Chapter 6). Stomach rupture has been reported as a cause of death in PWS due to overeating,<sup>77</sup> and surgically decreasing the size of the stomach may further increase the risk for the stomach to rupture. Therefore, these surgical procedures are not recommended at this time in subjects with PWS.

As concluded, obesity is the most significant health problem in PWS and is an increasingly common trait affecting one half of the general adult population in the United States.<sup>63,81</sup> It is on the rise in children with dramatic increases during the past decade. Obesity is a risk factor in five of the top 10 causes of death (heart disease, stroke, diabetes, atherosclerosis, and malignancies) in this country. There are several genetic syndromes besides PWS with obesity as a major component. These include: Cohen, Bardet-Biedl, Albright hereditary osteodystrophy, Borjeson-Forssman-Lehmann, Alstrom, Carpenter, and fragile X syndromes; cytogenetic or chromosome syndromes (e.g., 1p36 deletion, Smith-Magenis syndrome, Down syndrome, sex chromosome aneuploidy); and mutations of several obesity-related genes (e.g., leptin, leptin receptor, melanocortin 4-receptor, pro-opiomelanocortin [POMC], prohormone convertase-I, peroxisome proliferator-activated receptor-gamma, and beta-3 adrenergic receptor).<sup>10,37</sup> However, because of the substantial body of research on PWS and a prevalence rate higher than most, PWS is the best example of an obesity syndrome to study in order to gain a better understanding of the genetics of obesity, as well as behavioral dysfunction, and genotype/phenotype correlations.

## Other Medical Findings

### Bone Density

Other health concerns in individuals with PWS include reduced bone density and osteoporosis, which may lead to fractures.<sup>26,41,114</sup> Bone mineral density is a function of a dynamic process of bone resorp-

tion and production of mineralized bone matrix. The degradation of bone matrix or collagen can be determined by measuring urinary N-telopeptides of type I collagen, while total bone mineral content and body composition (e.g., percent fat) can be determined by dual energy X-ray absorptiometry (DXA). Butler et al.<sup>26</sup> reported data on bone density, anthropometric measurements, and biochemical markers of bone turnover in subjects with PWS or simple obesity. Significantly decreased total bone and spine mineral density and total bone mineral content in PWS subjects (ages 10–44 years) were found compared with normative data and similarly aged controls. However, no significant difference in urinary N-telopeptide levels was found between the PWS subjects and obese controls. This suggested a possible lack of depositing bone mineral during growth, when bones should become more dense (e.g., in adolescence), more so than bone loss in the subjects with PWS. This may be due to decreased production of sex or growth hormones and/or long-standing hypotonia with decreased physical activity.

### **Oral and Dental Issues**

Dental or oral findings have received limited study in PWS. Thick, sticky saliva is a consistent finding detectable during the neonatal period in PWS subjects regardless of the genetic subtype. Therefore, the gene(s) causing the salivary problem may be influenced by genetic imprinting. Salivary flow in PWS subjects is approximately 20% of that reported in controls.<sup>79</sup> Therefore, xerostomia or a dry mouth is frequently seen in PWS subjects. The salivary ions and protein are present in increased amounts, which may reflect a concentration effect relative to decreased water in the saliva.

Normal salivation produces a buffering capacity, induces clearance of substances in the mouth by swallowing, protects the teeth from extrinsic and intrinsic acids that initiate dental erosion, and allows for a capacity to remineralize partially demineralized enamel.<sup>139</sup> Therefore, syndromes with salivary dysfunction such as PWS predispose to tooth wear and underline the importance of normal salivation in the protection of teeth against wear by erosion, attrition, and abrasion. Dental malocclusion of varying degrees frequently occurs in PWS and may require orthodontic alignment. An altered craniofacial development and maxillary hypoplasia appears to predispose to dental malocclusion and possibly a narrow upper airway. The role of the dentist is considered important to monitor and treat the dental problems frequently seen in PWS. Additional oral findings are discussed in Chapter 6.

### **Growth and Growth Hormone**

Growth in people with PWS is generally characterized by initial failure-to-thrive, which may require gavage or tube-feeding during stage one of development, followed by a period of normal growth rate with heights below the 50th centile and often below the 10th centile. The lack of a growth spurt during adolescence results ultimately in mild short stature in both males and females. Without growth hormone

treatment, adult males with PWS are generally no taller than typical females in relationship to normative data. Bone age is generally delayed but may be normal or advanced. However, observed delays or accelerations of bone age generally return toward normal during adolescence or adulthood.

Intrafamilial and midparental PWS correlations and heritability estimates of anthropometric or physical variables from PWS subjects and their parents were undertaken by Butler et al.<sup>27</sup> in order to determine the effects of the genetic background on several growth parameters in this syndrome. The data suggested that taller parents with longer foot length have taller-than-average PWS children with longer feet. These physical characteristics are apparently influenced by the genetic background, while soft tissue parameters such as arm and calf circumferences and skinfolds showed lower heritability estimates.

Growth hormone deficiency or insufficiency is now recognized as a key feature of PWS and will be discussed in major detail elsewhere. However, one study of children with PWS showed that 98% had subnormal growth hormone levels over a 24-hour period, and 91% displayed subnormal response to growth hormone stimulation.<sup>3</sup> This insufficiency affects both stature and body composition in PWS subjects. Individuals with simple obesity without PWS also show reduced growth hormone secretion during provocative testing when compared with non-obese subjects, but the growth hormone insufficiency in PWS is not considered to be secondary to obesity. Individuals with simple obesity tend to be taller than normal due to elevated levels of another growth-promoting protein produced by the liver called insulin-like growth factor I (IGF-I).<sup>87</sup> IGF-I is low in children with PWS.<sup>96,112</sup>

Early studies in the 1980s of growth hormone replacement in children with PWS provided strong evidence that growth velocity was substantially improved. Treatment with growth hormone doses of 0.125 mg/kg/week showed an increased growth rate of 130%, 300%, and 600% of baseline in 3 of 4 treated children with PWS.<sup>95</sup> This study allowed for larger and more rigorous investigations of PWS subjects, which further delineated the presence of growth hormone insufficiency in children with PWS and provided convincing evidence that growth hormone replacement not only increases stature but also improves lean muscle mass, decreases body fat, increases exercise capacity and physical activity, and improves respiratory function. For example, a 25% reduction in total body fat was achieved with a corresponding 30% increase in fat-free mass, measurable by DXA and bioelectrical impedance, in children with PWS.<sup>96</sup> In addition, some parents reported improved behavior in their child with PWS undergoing growth hormone therapy, although additional long-term studies are needed. The positive changes in body composition (Figure 1.5, see color insert) appear to be due to growth hormone treatment and not due to changes in caloric intake or exercise regime. Potential side effects have been recognized, including the risk for Type 2 diabetes mellitus and worsening of scoliosis in PWS subjects. Growth hormone appears to have a





**Figure 1.5.** Five-year-old boy with Prader-Willi syndrome before (top) and after 3 months of growth hormone (GH) treatment (bottom). Note the improved body habitus, muscle bulk, and reduced fat. The patient was able to increase total caloric intake, and he had increased activity and wakefulness. Reprinted with permission from S.B. Cassidy, "Prader-Willi syndrome in the new millennium: introduction," *The Endocrinologist* 2000;10(4) Suppl 1: 1S–2S. Copyright©2000 by Lippincott Williams & Wilkins. (See color insert.)



high level of safety in the child with PWS and holds promise for potential benefits in adults with the syndrome not previously treated with growth hormone, although there is a paucity of data in adults. Additional information regarding use, benefits, and potential side effects of growth hormone treatment will be described in more detail elsewhere (see Chapter 7).

Many clinical features in PWS support growth hormone deficiency, which has been documented by a low peak growth hormone response to provocative stimulation tests, decreased random growth hormone secretion, and low serum insulin-like growth factor-I (IGF-I) levels in several studies in over 300 affected children.<sup>14</sup> Additionally, 40% to 100% of children with PWS have fulfilled the criteria for growth hormone deficiency, which is generally defined as a peak growth hormone level of less than 10 micrograms/liter in response to one or two stimulation tests. Along with insufficient growth hormone secretion, PWS subjects have a dysfunctional hypothalamic-pituitary-gonadal axis, which may contribute to thermoinstability and a high pain threshold and appears to play a role in the abnormal appetite and incomplete sexual development. This axis and disturbances seen in PWS will be discussed in more detail elsewhere (see Chapter 5).

### Blood Studies

Both normal and elevated levels of cholesterol and lipids have been reported in subjects with PWS.<sup>7,11,36,94</sup> Amino acid levels have also been reported to be normal in PWS subjects.<sup>34</sup> For example, Butler et al.<sup>36</sup> reported a comparison study of plasma lipid, cholesterol, glucose, and insulin levels in 26 subjects with Prader-Willi syndrome (deletion and nondeletion) and 32 individuals with simple obesity. The average percentage of ideal body weight (IBW) for the reported PWS group was  $175.6 \pm 68.0$  compared with  $150.3 \pm 43.8$  for the obese subjects. Fasting plasma lipid, glucose, and insulin levels were not significantly different between the two subject groups, but insulin levels were higher than the normative non-obese ranges. However, no significant correlations in lipid levels were found in subjects with PWS (deletion or nondeletion) compared with obese individuals for either age or percentage of IBW. No consistent abnormalities were reported in fasting plasma amino acid or urine organic acid levels in PWS subjects compared with obese controls, and similarly for thyroid hormone, spontaneous cortisol, and ACTH levels. Basal prolactin levels were reported within the normal range in PWS subjects. However, plasma gamma amino-butyric acid (GABA), dehydroepiandrosterone (DHEA), and DHEA-sulfate levels were reportedly elevated in PWS subjects.<sup>14,47,60</sup>

Butler et al.<sup>25</sup> reported a 6-year-old PWS male with maternal disomy 15 and ethylmalonic aciduria, which raised the question of an inborn error of metabolism, particularly a mitochondrial abnormality. Fasting plasma coenzyme Q10, an oxygen scavenger utilized in the mitochondria or the power plant of the cell for the electron transport chain involved in cellular metabolism and energy expenditure, was measured in PWS subjects and compared with obese and non-obese sub-

jects.<sup>24</sup> No significant differences were found in the coenzyme Q10 levels in PWS subjects compared with similarly aged obese subjects; however, lower coenzyme Q10 levels were found in the PWS subjects compared with non-obese controls. The role of the mitochondria in decreased energy expenditure and the lower metabolic rate in PWS will require further testing.

### Brain Studies

Although most autopsy studies in PWS subjects have been unremarkable, recent reports have suggested that the paraventricular nucleus (a region of the brain involved in the control of appetite and sexual behavior) may be reduced in size, with fewer oxytocin-expressing neurons. Further studies by Swaab<sup>121</sup> showed a 30% reduction in the growth hormone releasing hormone (GHRH) neurons in the arcuate nucleus, a key brain region for the release of neuropeptides involved in eating behavior. These changes in the hypothalamic region may be sufficient to impair the regulation of food intake and may be the result of a defective protein (or lack of a protein) due to the chromosome 15 abnormality and interference in gene regulation. This protein derangement may interfere with several systems through gene transcription errors, thereby affecting a regulatory protein impacting on neurotransmitter or neurohormone levels. An example is the *SNRPN* gene, which is expressed in the brain and involved with splicing messenger RNA. This paternally expressed gene is found in the 15q11–q13 region and deleted in the majority of PWS subjects or with lack of expression in those with maternal disomy. This loss may impact on the function of the hypothalamus and lead to altered hypothalamic neuron and neuroendocrine function. The differential expression of a second gene called *7B2* in the hypothalamus of subjects with PWS may also be affected by this genetic derangement.<sup>67</sup> However, the gene expression for ghrelin, peptide YY, and their receptors was studied and found to be present in brain tissue from both PWS and control subjects.<sup>124</sup>

The product of gene *7B2* is a neuroendocrine chaperone protein that interacts with prohormone convertase PC2, involved in the regulated secretory pathway in the brain impacting on function. The *7B2* gene is located in the 15q13–q14 region, close to the 15q11–q13 region involved in PWS. Therefore, alteration of the 15q11–q13 region (e.g., deletion) may impact on regulation or activity of the *7B2* gene in PWS subjects, as recently reported.<sup>8,9</sup> Hence, Gabreels et al.<sup>67</sup> studied the presence of the neuroendocrine *7B2* protein in the supraoptic and paraventricular nucleus of the hypothalamus of five subjects with PWS using antibodies against various segments of the *7B2* precursor polypeptide. Three of the five PWS subjects showed no reaction to the *7B2* antibody, MON-12, while 30 control subjects showed a positive reaction. Thus, there was a clear modification of *7B2* expression in some PWS subjects, indicating altered neuroendocrine function. In a similar report, these authors showed no antibody reaction in these brain nuclei against processed vasopressin, another brain-released hormone, but did show reactivity against the vasopressin precursor.<sup>66</sup> Preliminary molecular

genetic data on the 7B2 gene in eight individuals with PWS showed abnormalities (M.G. Butler, unpublished data), but additional studies are warranted. In addition, preliminary genome-wide expression using gene microarray technology showed over- and underexpression of dozens of lipid metabolism and neurodevelopmental genes, when comparing brain and somatic tissue of PWS subjects matched with controls (M.G. Butler, unpublished data).<sup>8,9,124</sup>

Positron emission tomography (PET) scans and magnetic resonance imaging (MRI) studies in PWS have revealed disturbances in the hypothalamic region of the brain, suggesting possible dysfunction.<sup>29</sup> Additionally, abnormal cortical development was reported using 3-D MRI in PWS subjects.<sup>138</sup> Specialized proton magnetic resonance spectroscopy (MRS) of the brain in subjects with PWS and MRI images revealed mild abnormalities including slight ventriculomegaly, cortical atrophy, and a small brain stem. Other methods to examine brain chemistry and metabolites include N-acetylaspartate choline (NAA/Cho) and N-acetylaspartate/creatine (NAA/Cr) ratios, which were decreased in subjects with PWS, although the Cho/Cr ratio did not differ from control subjects. Thus, neuron loss or dysfunction was suggested in PWS.<sup>80</sup> Parietal lobe pathology detected on 1H-magnetic resonance spectroscopy may also be associated with more global brain damage and loss of cognitive function.

## Cognitive and Behavioral Findings

Decreased intellectual functioning was among the four original defining characteristics of PWS.<sup>55,110,140</sup> IQs have ranged from 12 to 100 in previous studies in PWS,<sup>32,49,59,75,88,140</sup> but the average IQ is typically in the mild range of intellectual disability (55–70 IQ). The distribution includes a few reports within the 85–100 IQ range and other reports within the profound-to-severe range of mental retardation (IQ < 40). Greenswag<sup>72</sup> reported the IQ in a large survey of PWS subjects and found that IQ was greater than 85 in about 5% of subjects, about 25% had borderline mental retardation, 35% had mild retardation, 25% had moderate mental retardation, and about 5% had severe mental retardation.

Although approximately 30% of PWS individuals have IQs in the normal or borderline range, cognitive dysfunction is nearly always present. However, body weight may correlate with IQ in PWS individuals. For example, Crnic and colleagues<sup>49</sup> reported that individuals with PWS who were never obese had significantly higher IQ scores (mean = 80.2) than PWS subjects who were currently obese (mean = 57.3) or had been obese and lost weight (mean = 59.9).

Interestingly, individuals with PWS may have greater-than-expected abilities to recognize and evaluate figures and shapes and strengths in tasks requiring integration of stimuli in a spatial relationship. The reports of superior puzzle-solving ability in PWS individuals would be consistent with this observation.<sup>56,84</sup> Dykens<sup>56</sup> studied children with PWS in order to characterize their presumed ability at jigsaw puzzles. She reported relative strengths on standardized visual-spatial tasks

such as object assembly, and the scores were significantly higher in PWS subjects compared with age- and IQ-matched control subjects with mixed mental retardation, but below those of age-matched normal children with average IQs. In contrast, children with Prader-Willi syndrome scored similarly to normal peers on word searches and outperformed them on jigsaw puzzles, placing more than twice as many pieces as the typically developing group.

Warren and Hunt<sup>135</sup> found that children with PWS performed less well on a picture recognition task than children with mental retardation of unknown etiology matched for chronological age and IQ. The two groups of children performed similarly on a task meant to measure access to long-term memory. There are few studies on learning and memory in PWS, although it is thought that children with PWS have a deficit in short-term visual memory but not in long-term visual storage.<sup>135</sup> As mentioned earlier, visual perception, organization, and puzzle-solving skills are reported as relative strengths in some people with PWS, including stronger visual memory in the PWS subjects with maternal disomy compared with those with typical deletions<sup>89</sup> (see section on Genotype-Phenotype Relationships, below).

Early studies have reported that reading abilities may be better than arithmetic abilities in most PWS subjects, although both are deficient.<sup>120</sup> Greenswag<sup>72</sup> reported that 75% of 232 PWS individuals analyzed had received special education services and typically performed at the sixth grade or lower level in reading and at the third grade or lower in mathematics. Reading problems in PWS may be exacerbated by visual perceptual deficits, particularly in the maternal disomy subjects. While PWS individuals with typical deletions usually have a lower verbal IQ, those with maternal disomy exhibit a deficit in visual processing on some tasks, which may offset their greater verbal ability. However, Dykens et al.<sup>59</sup> reported that adolescents and adults with PWS have overall standard academic achievement scores higher than their ability measures. In addition, a study by Kleppe et al.<sup>90</sup> revealed multiple articulation errors (dysarthria), reduced intelligibility, and delayed language skills (vocabulary, syntax, and morphologic abilities) in children with PWS.

Dykens et al.<sup>59</sup> reported that daily living skills may change with increasing age in PWS. Thompson and Butler (unpublished data) found that PWS subjects and IQ-matched controls differed substantially in their degree of independent community living skills. The PWS subjects appeared significantly less competent than controls. While this may indicate biologically-based differences in cognitive ability, it may also reflect the far more restricted lives that most individuals with PWS lead (and therefore more limited opportunities to develop skills) due to the concerns that caregivers have about access to food in uncontrolled settings.

Butler, Thompson, and colleagues<sup>126</sup> collected clinical, genetic, cognitive, academic, and behavioral data from 49 individuals with PWS (22 males, 27 females; 27 with the typical 15q deletion, 21 with maternal disomy 15, and 1 with an imprinting defect), ranging in age from 10 to 50 years, and 27 control participants. We found that PWS participants

obtained significantly lower scores than control subjects in performance IQ ( $p < 0.05$ ), visual-motor skills ( $p < 0.01$ ), and adaptive functioning as assessed by the broad independence ( $p < 0.01$ ), community independence ( $p < 0.01$ ), and motor skill ( $p < 0.001$ ) dimensions of the Scales of Independent Behavior. No significant differences were found for measures of academic achievement. With respect to maladaptive behaviors, PWS participants demonstrated significantly higher levels of self-injury on the Reiss ( $p < 0.05$ ) and higher scores on the general maladaptive index ( $p < 0.05$ ) of the Scales of Independent Behavior, indicating worse behavior.

### **Behavioral Issues**

Several behavioral and psychological findings can be present in individuals with PWS including temper tantrums, stubbornness, hoarding, 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.<sup>40,72,75,84,120,137</sup> Individuals with PWS are generally more verbally aggressive and self-assaultive, but less sexually inappropriate, than study controls. Children with PWS may be more immature and clumsy and more likely to be disliked and teased by their peers.<sup>131</sup> However, they also can be caring and affectionate. Not all individuals with PWS will have the behavior problems that have been reported. A further description and discussion of the behavioral characteristics will be presented elsewhere (see Part III).

#### ***Self-Injurious Behavior***

Skin picking and other forms of self-abusive behavior are found at some time in most persons with this syndrome and also can be seen in individuals with autism and other related developmental disorders. Infections in the involved skin areas can occur. Occasionally, an area may be picked for several years. Serious health problems from persistent self-injury may occur and include eye poking, subdural hemorrhage from forceful head banging, infections from self-inflicted skin picking, and anorectal disease from rectal picking and digging.<sup>5</sup> Studies may reveal one or more ulcers in the rectum, which can be confused with inflammatory bowel disease.

Self-injurious behaviors can be among the most clinically problematic behaviors associated with Prader-Willi syndrome. Previous studies have found self-injurious behavior (most notably skin picking) to be a prevalent behavioral problem in 69% of adolescents with Prader-Willi syndrome<sup>137</sup> and in 81% of adults.<sup>129</sup> Symons et al.<sup>122</sup> surveyed families of 62 persons (24 males, 38 females; mean age of 18 years; age range 3 to 44 years) with Prader-Willi syndrome and determined the prevalence, topographies, and specific body locations of self-injurious behavior. Self-injury was reported for 81% of the participants, with over 800 self-injury body sites recorded. Skin picking was the most prevalent form of self-injury (82%), followed by nose picking (28%), hand biting (17%), head banging (14%), hair pulling (9%), and rectal picking (6%).



The front of the legs and head were disproportionately targeted as preferred self-injury body sites.

Among school-age students with mental retardation, Symons et al.<sup>122</sup> found that the most common forms of self-injury were biting, head banging, and hitting, whereas picking and pinching were more common among the PWS subjects. Non-PWS individuals with mental retardation tend to direct self-injury toward the head, while PWS subjects tend to distribute self-injury widely across the body including specific finger, arm, and leg areas. Other forms of self-abusive behavior have been reported, including trichotillomania, pushing pins and tacks into skin, and pulling out nails.<sup>5</sup> Onset of these behaviors is variable, usually during childhood but sometimes not until adolescence or early adulthood.

The etiology and pathophysiological mechanisms of self-injury are poorly understood. The primary pharmacological approaches for treating self-injury in persons with mental retardation and related developmental disabilities are aimed at the dopaminergic system (i.e., neuroleptics), the serotonergic systems (i.e., serotonin reuptake inhibitors), or the endogenous opioid peptide systems (i.e., opiate antagonists).<sup>6,128</sup> Some pharmacological approaches to treating self-injury among persons with Prader-Willi syndrome have been useful.<sup>119,134</sup>

### ***Compulsive Behavior***

Dykens et al.<sup>58</sup> reported that compulsive symptoms are found in up to 60% of persons studied with PWS. Obsessive-compulsive disorder (OCD)<sup>32,72</sup> symptoms usually begin in adolescence or adulthood in the non-PWS population, and the compulsive behaviors are believed to reduce or prevent anxiety. A large body of evidence has implicated serotonergic mechanisms as underlying the clinical manifestations of OCD in other neuropsychiatric populations.<sup>103</sup> Pharmacologic agents that inhibit serotonin reuptake (e.g., clomipramine) have produced clinical improvements as well as changes in peripheral measures of serotonin function,<sup>62</sup> and use of these agents has improved compulsivity and reduced OCD symptoms in some individuals with PWS.<sup>51,82</sup> Similarities in the number, type, and severity of compulsive behaviors in adults with PWS and those with OCD have been reported.<sup>59</sup> However, compulsive behavior in typically developing children decreases from 2 to 6 years, while compulsivity increases in children with PWS during this age range.<sup>52,53</sup> There appears to be a temporal correlation between appetite onset and compulsivity and tantrums in children with PWS. While people with PWS have compulsive disorder that overlaps with that seen in other conditions (e.g., OCD, autism), it may also involve different mechanisms.

On the Yale-Brown Obsessive Compulsive Scale (Y-BOCS), Butler, Thompson, and colleagues<sup>126</sup> found group differences between PWS and control participants for the total ( $p < 0.05$ ) and compulsions ( $p < 0.01$ ) scores, as well as for specific aspects of severity of compulsions: time spent performing compulsions ( $p < 0.01$ ), length of compulsion-free intervals ( $p < 0.01$ ), interference with daily activities ( $p < 0.01$ ), and degree of control over compulsions ( $p < 0.01$ ). In contrast, significant



group differences were not obtained for any Yale-Brown Obsessive Compulsive Scale obsession scores, or for internal aspects of compulsive behaviors, such as the individual's effort to resist against compulsions.

It appears that people with PWS have a compulsive disorder related, but probably not identical, to compulsive disorder seen in other conditions such as autism, Tourette's syndrome, and obsessive-compulsive disorder alone. We further speculate that lack of GABA-ergic inhibition of dopaminergic and serotonergic neurons in the orbitofrontal and prefrontal cortex and head of the caudate nucleus may be implicated in the compulsive symptoms seen due to the following: (1) the presence of three GABA-A receptor genes (alpha 5, beta 3, gamma 3) in the chromosome 15q11-q13 region; (2) our findings of elevated levels of GABA in plasma of individuals with PWS and Angelman syndrome (as previously indicated, possibly reflecting up-regulation of GABA due to improper binding at GABA receptors); and (3) recent gene expression studies with paternal bias of the GABA receptor genes.<sup>8,9</sup> There are reports that psychotropic medications reduce obsessive-compulsive disorder symptoms in other people and tend to reduce tantrums and compulsive behavior in people with PWS,<sup>51, 119, 134</sup> but this area has been poorly studied in PWS.

## Genotype-Phenotype Relationships

### Clinical, Behavior, and Cognition

Phenotypic clinical differences among individuals with Prader-Willi syndrome having separate genetic subtypes (typical deletion, maternal disomy, or imprinting defect) are important to study to learn about the role of specific genes and their clinical outcomes. The correlation of specific clinical manifestations and genetic findings will enhance our understanding of genomic imprinting and genotype/phenotype correlations in PWS. The rarity of individuals with imprinting defects has limited their comparison to those individuals with typical deletions or maternal disomy for genetic and clinical correlation studies.

The phenotypic spectrum of PWS is quite variable and may be dependent on the genetic subtype. In addition, genotype/phenotype differences may be helpful in guiding the clinician in the evaluation of patients with suspected PWS and in providing prognostic counseling for families once the diagnosis (and specific genetic subtype) of PWS is established.

Hypopigmentation (i.e., lighter hair, eye, and skin colors compared with other family members at a similar age) has been noted to occur at a higher frequency in PWS subjects with the typical chromosome 15 deletion<sup>16,17,32</sup> and is found to be associated with a deletion of the *P* gene, which is involved in pigment production, localized at the distal end of the chromosome 15q11-q13 region. Molecular genetic studies have shown that hypopigmentation does not correlate with the DNA haplotype pattern in the region of the *P* gene.<sup>118</sup> In addition, the *P* gene is not considered to be imprinted and is expressed in both chromosome 15s

but deleted from one member of the pair in PWS (and AS) subjects with the typical 15q11–q13 chromosome deletion, leading to a decreased amount of pigment.<sup>8,9</sup>

Previous studies have revealed that individuals with PWS with the chromosome 15 deletion were more homogeneous than other PWS subjects in their clinical presentation and anthropometric or physical measurements (e.g., radiographic measurements of the bones of the hand), as reflected in the metacarpophalangeal pattern profile.<sup>28</sup> Those with the 15q deletion (males and females) also were more homogeneous than nondeletion subjects with respect to dermatoglyphic plantar findings of the foot, with a lack of plantar interdigital II–IV patterns with almost exclusively hallucal distal loops.<sup>111</sup> Early studies were conducted before the recognition of maternal disomy 15 as the most common cause of the nondeletion status among people with PWS.

With the advent of molecular testing for all subjects with PWS, several studies have been reported to compare the major genetic subtypes (deletion and maternal disomy) with clinical findings. For example, Gillessen-Kaesbach et al.<sup>68</sup> noted lower birth weights in individuals with PWS and the typical deletion subtype, while an increased maternal age was found in the case of those with maternal disomy. This latter observation was consistent with the source of the extra chromosome 15 from the mother during egg production causing trisomy 15, or three chromosome 15s in the fetus, followed by loss of the chromosome 15 donated from the father during early pregnancy, leading to maternal disomy 15 in the fetus at birth. Mitchell et al.<sup>102</sup> also reported a shorter birth length in PWS males with maternal disomy, compared with males having the 15q deletion, and a shorter course of gavage feeding with a later onset of hyperphagia in PWS females with maternal disomy. In addition, Cassidy et al.<sup>44</sup> observed that people with PWS and maternal disomy were less likely to have the typical facial appearance and less likely to show certain behavioral features of PWS, including skin picking, skill with jigsaw puzzles, a high pain threshold, and articulation problems. No significant differences were found between the groups (deletion and maternal disomy) in most other clinical findings including neonatal hypotonia, need for gavage feeding, cryptorchidism, genital hypoplasia, small hands and feet, scoliosis, dental anomalies, sticky saliva, behavioral disturbances, hyperphagia, decreased vomiting, or sleep disorder. Gunay-Aygun et al.<sup>73</sup> reported that the diagnosis of PWS among individuals with maternal disomy was typically reported later than among those with a deletion, possibly due to a milder phenotype in maternal disomy subjects.

People with PWS may hoard and arrange items excessively. Dykens et al.<sup>57</sup> described differences between the genetic subtypes in PWS subjects such that the deletion group had higher scores using the Child Behavior Checklist, indicating more compulsive symptoms and more symptom-related distress. In addition, Symons et al. characterized the self-injurious behavior in 62 PWS subjects via a questionnaire survey.<sup>122</sup> PWS individuals with the typical 15q11–q13 deletion injured at significantly more body sites than did individuals with maternal disomy 15. Skin picking was the most common form of self-injury. Thompson and

Butler<sup>126</sup> found that PWS subjects with typical deletions exhibited significantly greater self-injury than both a control group and a maternal disomy subgroup. The typical deletion subgroup also displayed higher compulsivity scores than the control group and spent more time engaging in compulsive behavior. Their compulsive rituals interfered with their daily living, and they were less able to control their compulsive behavior. Both PWS genetic subgroups showed significantly greater global severity of compulsive behaviors than the control group, while the typical deletion group consistently showed the most severe symptoms of OCD. Subjects with maternal disomy showed an intermediate level of OCD symptoms. Additional studies will be needed to confirm this observation. In addition, Vogels et al.<sup>132</sup> recently reported that psychoses in Prader-Willi syndrome subjects occur more often in those adults with maternal disomy 15 compared with those with the deletion.

Subgroup comparisons in a study by Roof, Butler, Thompson and others<sup>113</sup> revealed additional differences between PWS deletion and maternal disomy participants in measures of intelligence and academic achievement administered to 38 individuals with PWS (16 males and 22 females; 24 with deletion and 14 with maternal disomy). PWS subjects with maternal disomy 15 had significantly higher verbal IQ scores than those with the deletion ( $p < 0.01$ ). The magnitude of difference in verbal IQ was 9.1 points (69.9 versus 60.8 for maternal disomy and deletion PWS subjects, respectively). Only 17% of the subjects with the 15q11-q13 deletion had a verbal IQ  $\geq 70$ , whereas 50% of those with maternal disomy had a verbal IQ  $\geq 70$ . However, performance IQ scores did not differ between the two PWS genetic subtype groups (62.2 versus 64.7 for maternal disomy and deletion PWS subjects, respectively). The full scale IQ did not differ significantly between the two groups (64.1 versus 61.0 for maternal disomy and deletion, respectively). Specific subtest differences were noted in numeric calculation skill, attention, word meanings, factual knowledge, and social reasoning, with the maternal disomy PWS subgroup scoring higher than the typical deletion subgroup. Deletion PWS subgroup subjects scored higher than the maternal disomy subgroup on the object assembly subtest, which further supports specific visual-perceptual skills being a relative strength for the deletion subgroup. This may explain anecdotal accounts of subjects with PWS having an uncanny ability to assemble jigsaw puzzles and the study reported by Dykens.<sup>56</sup> Dykens found that, within Prader-Willi syndrome, puzzle proficiency was not predicted by age, IQ, gender, degree of obesity, or obsessive-compulsive symptoms but by the genetic status (specifically higher in the deletion subgroup).

The mechanisms whereby certain skills appear to be preserved in the maternal disomy subgroup have yet to be identified. Whether this phenomenon is caused by genomic imprinting versus the nonimprinting status of genes in the 15q11-q13 region is not known. The presence of more active or expressed genes in maternal disomy individuals may be due to possible dosage mechanisms. If only one allele, or member of a gene pair, is normally expressed (i.e., one allele is active on the

mother's chromosome 15 but inactive on the father's chromosome 15), and there are two active copies instead of one copy (e.g., maternal disomy 15), then more gene product is produced, which may be advantageous. Evidence to date further documents the difference between verbal and performance IQ score patterns among subjects with PWS and the deletion versus the maternal disomy subtype.

### Visual Perception and Visual Memory

Discrimination of shape of motion testing was performed by Fox et al.<sup>65</sup> wherein forms were generated by random dot elements that varied in element density and temporal correlation. This testing was done in four participant groups (PWS deletion, PWS maternal disomy, comparison subjects, and normal controls). The procedure uses white dots presenting on a computer monitor that blink on and off randomly. Imbedded within the randomly presented dots is a fixed array of dots with a defined form (e.g., the letter "E"), moving slowly from side to side. The array may vary in element density and degree of correlation of the blinking dots. Performances of normal controls exceeded that of all other groups (78% correct,  $p < 0.009$ ). The typical PWS deletion (66%) and equivalent controls (59%) did not differ significantly. However, performance of the maternal disomy group was significantly worse (38%) than any of the other groups ( $p < 0.04$ ). The inferior performance of the maternal disomy group may be attributed to receiving two active alleles of maternally expressed genes influencing development of the visual system. Other possibilities include the requirements of paternally expressed genes, residual mosaic trisomy in brain tissue, or complex interactions including specific ratios of differentially spliced gene products.<sup>65</sup> Alternatively, since we know people with PWS have elevated plasma GABA, and it has been shown from other studies that excessive GABA levels have deleterious effects on retinal functioning, it is possible that visual signal strengths could be compromised at the level of initial input, which would manifest itself as a perceptual deficit.

Joseph et al.<sup>89</sup> reported substantial differences in visual-spatial memory among PWS individuals with maternal disomy compared with those with deletions. The rate of short-term memory decay among individuals with maternal disomy was considerably slower than in either PWS individuals with typical deletions or matched controls. The study involved 17 individuals with PWS—7 with deletions, 10 with maternal disomy—and 9 matched controls. Each participant performed a visual recognition task. A series of color digital photographs was presented; most were presented twice, and the remainder appeared only once. Photographs presented twice were separated by 0, 10, 30, 50, or 100 intervening photographs. After viewing each photograph, participants indicated whether or not the photograph had been presented previously. This procedure was conducted twice, once using photographs of foods and the second time using non-food items. As the number of intervening photographs increased between the first and second presentation, participants were less likely to remember having

seen the photograph previously. Performance by the maternal disomy participants was less affected by increasing the number of intervening photographs relative to the other two groups (deletion and non-PWS controls), suggesting superior visual recognition memory.

### Phenotypes Associated with Longer Versus Shorter Typical Deletions

The majority of people with PWS have a paternally derived interstitial deletion of the 15q11–q13 chromosome region including 3.5 million to 4 million base pairs of DNA. Two proximal breakpoints (BP1 and BP2) where the typical deletion occurs have been reported in this region. Type I deletions (involving BP1) are larger than type II deletions (involving BP2) by about 500 kilobases of DNA.<sup>130</sup> Clinical, anthropometric, and behavioral data were analyzed in 12 PWS subjects (5 males, 7 females; mean age  $25.9 \pm 8.8$  years) with type I deletion and 14 PWS subjects (6 males, 8 females; mean age  $19.6 \pm 6.5$  years) with type II deletion, determined by presence or absence of DNA markers between BP1 and BP2.<sup>20</sup> PWS subjects with the longer typical deletions scored significantly higher in tests measuring self-injurious and maladaptive behaviors compared with PWS subjects with shorter typical deletions. In addition, obsessive-compulsive behavior was more evident in PWS subjects with longer deletions. It appears that loss of genetic material between breakpoints BP1 and BP2 significantly increases the severity of behavioral and psychological problems in this syndrome. Four genes have been identified and located between BP1 and BP2.<sup>46</sup> They may play a role in brain development or function accounting for our observed clinical differences. One of those genes, *NIPA-1*, is expressed in brain tissue and will require further investigation to determine its role in causing specific clinical findings in PWS.

### Conclusions

Prader-Willi syndrome is a prototypic contiguous gene disorder with several genes in the 15q11–q13 region contributing to the phenotype. PWS and Angelman syndrome were the first examples in humans of genomic imprinting, or due to the difference of genetic expression depending on the parent of origin. Significant behavioral differences distinguish the two major genotypes (typical deletion versus maternal disomy). Generally, those with typical deletions of the entire region have had the most severe behavioral phenotype with more skin picking, lower verbal IQ, and hypopigmentation. Those with maternal disomy are more impaired on visual perception but have superior visual recognition memory. We have recently found that among those with typical deletions, there are two subtypes, a longer (type I) and shorter (type II) deletion. The phenotypes of individuals with the longer deletion are more severe in general than those with shorter deletions. Within the region between the longer and shorter deletion breakpoints is the *NIPA-1* gene, which is expressed in brain tissue and may be implicated in these differences.<sup>20</sup>

Many features in persons with PWS suggest a hypothalamic dysfunction: hyperphagia, sleep disorders, deficient growth hormone secretion, and hypogonadism. In addition, children with damage to the hypothalamus such as following craniopharyngioma brain tumor surgery can show features similar to PWS including an increased appetite, obesity, learning and behavior problems, a decreased growth rate, and endocrine disturbances. This relationship should be further pursued in brain pathology and neuroanatomical studies including brain imaging (e.g., functional MRI and optical topography).

A multidisciplinary approach is needed to treat individuals with PWS, regardless of the age of the patient. Primary care physicians such as pediatricians, family physicians, or internists should be able to treat most patients with PWS in consultation with a clinical geneticist, endocrinologist, dietitian, and other experts as needed. Additional information about PWS can be obtained by contacting a local genetics center and through the national and local Prader-Willi syndrome associations.

Most individuals with this syndrome can be healthy if diagnosed early and a treatment plan is in place to avoid the complications of uncontrolled obesity. Additional needs depend on the overall health of the child and the age at diagnosis. Exercises to increase coordination, balance, and strength are important but should be kept simple and low in number at the beginning and gradually increase over time. Consultation with the patient's doctor and physical therapist is recommended before undertaking an exercise program at home or in the school setting. A better understanding of energy expenditure and energy balance in PWS is clearly needed.

There are currently no consistent, well-established behavioral or psychological management methods for overcoming all behavioral problems associated with PWS. The greatest success appears to be obtained by capitalizing upon the inherent compulsivity of people with PWS in devising highly predictable daily routines, the use of behavior management reward systems to promote exercise and diet control, and providing choice whenever feasible within the structured daily schedule. Tasks to improve social skills such as taking turns or working together with peers may be useful. These tasks should be incorporated into the classroom setting by working closely with the school educators and administrators.

Selective serotonin reuptake inhibitors may be helpful in reducing tantrums, while atypical neuroleptics that produce minimal weight gain may be of some value in treating aggressive outbursts that may occur in some PWS individuals. Skin picking appears to be regulated by a different neurochemical mechanism than other compulsive symptoms, which may implicate the lack of GABA-ergic inhibition at the brain level. No systematic trials of GABA agonists have been reported to date. Pharmacological treatments for weight control and behavior problems have met with only modest results. A better understanding of genome-wide microarray expression in brain and peripheral tissues and recognition of disturbed interconnected gene pathways in PWS may lead to additional treatment modalities.



It is often difficult but vital to find appropriate services to meet the needs of the immediate and extended family as well as teachers. Since nearly one third of the people with PWS have a low normal IQ, they often do not qualify for mental retardation services yet are poorly served within most psychiatric programs. Many parents and advocacy organizations have developed specialized residential programs for young adults with PWS to meet this need.

With recent approval of growth hormone for treating individuals with PWS, many children are now on therapy and positive results have been reported, specifically with an increased muscle mass and strength, improved respiratory function, decreased fat mass, increased physical activity and energy expenditure, and taller stature. Potential side effects relating to growth hormone treatment are under long-term study in the PWS population. PWS subjects may have scoliosis, which could be exacerbated by rapid growth in children with or without PWS regardless of growth hormone treatment. Therefore, checking and monitoring for scoliosis should be performed by their physician on a regular basis before and while receiving growth hormone. Growth hormone treatment in non-PWS populations may be associated with an increased risk for slipped capital femoral epiphysis, a condition that is associated with obesity. Growth hormone treatment also may be associated with an increased incidence of pseudotumor cerebri. Thus, careful monitoring for these findings should be routine in following children with PWS.

Obesity is a major health problem in PWS with an increased risk for Type 2 diabetes mellitus in individuals with PWS and other complications related to obesity. Moreover, growth hormone treatment may decrease insulin sensitivity and further increase the risk for non-insulin-dependent diabetes mellitus. Therefore, all children with PWS and obesity should be carefully monitored for glucose intolerance and diabetes mellitus regardless of growth hormone treatment.

It is reasonable to believe that the improvement in body composition noted in children with PWS on growth hormone therapy should lower the risk for co-morbid diseases (e.g., diabetes, high blood pressure, cardiovascular disease). A long life span with a better quality of life would be anticipated. There is a high probability that the growth hormone/insulin growth factor axis deficiency seen in children with PWS is also present in adults. Therefore, adults may also benefit from growth hormone therapy, but there is a paucity of data in treating adults with PWS at this time. Understanding the genetic cause and pathophysiology of Prader-Willi syndrome should allow for better treatment options for the future and a better quality of life for those affected with this condition.

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# Part II

## Medical Physiology and Treatment

# Medical Considerations in Prader-Willi Syndrome

Urs Eiholzer and Phillip D.K. Lee

In the decade since the previous edition of this text,<sup>2</sup> a wealth of information has accumulated regarding the medical pathophysiology and treatment of PWS. Clinical diagnostic criteria and acceptance of genetic testing in the mid-1990s helped to focus clinical and research attention on individuals with this condition. The identification of a defect in the growth hormone (GH) system and, moreover, demonstration of GH treatment efficacy, provided the first and, to date, only treatment for PWS to attain regulatory approval.

Despite these advances, we still lack systematic information regarding many of the morbidities associated with PWS. Aside from GH-related studies, few rigorously-collected data on sufficient numbers of individuals have been published. Medical care for most individuals with PWS worldwide remains uncoordinated and clinical protocols are largely based on anecdotal experience. These circumstances are undoubtedly due to a combination of the uncommon occurrence of the condition, a relative paucity of specialized treatment facilities with consequent lack of centralized care and data collection, and historical prejudices and beliefs regarding natural history and treatment outcomes. Nevertheless, our understanding of the medical aspects of PWS has reached a new level in the past decade, and there are continuing efforts amongst experts in the field to establish logical, evidence-based treatment modalities.

Whereas the 1995 edition of this text contained only a single chapter concerning medical pathophysiology, entitled “Endocrine and Metabolic Aspects of Prader-Willi Syndrome,”<sup>127</sup> the current edition includes three chapters covering a wider range of medical concerns. This first chapter in Part II provides a general overview of medical concerns in PWS and discussion of conditions that are not addressed in successive chapters. The next chapter (Chapter 6) addresses issues related to obesity, gastrointestinal function, and body composition. Finally, Chapter 7 is dedicated to a review of GH therapy in PWS.

## Natural History and Age-Related Morbidity

The medical life history of a typical individual with PWS can be instructive in providing a logical framework for the succeeding discussions. Various “life stage” classifications have been proposed, all generally similar in terms of associated morbidities. The life-staging outlined here is primarily for the sake of illustration. In reality, most PWS-associated morbidities are part of a lifelong continuum.

The first stage is *in utero*. The most notable abnormality at this stage is fetal hypomotility, usually noted by women with previous non-PWS pregnancies. This hypomotility is consistent with hypotonia, a lifelong feature of the syndrome. In male fetuses with PWS, there is an increased risk for testicular maldescent but not other genital abnormalities. Scoliosis may also occur *in utero*, although this is uncommon in our experience. Hypogonadism and scoliosis, like hypotonia, are lifetime features of the syndrome. No other abnormalities have been noted during fetal life. No abnormalities of the placenta, umbilical cord, or amniotic fluid volume or composition have been reported. Increased fetal wastage has not been reported.

The neonate with PWS is usually born at or near term and no specific abnormalities of labor and delivery have been noted. A slightly low, but not usually abnormal, birth weight is characteristic. Cryptorchidism and scoliosis may be noted at birth, along with the characteristic facies and other features as described in preceding chapters.

The most striking medical abnormality in the neonatal period is severe whole-body hypotonia, a condition that is virtually universal for infants with PWS. Decreased limb movements, marked truncal hypotonia, weak cry, and decreased neuromotor reflexes are related characteristics. Dysconjugate eye movements (strabismus, but not nystagmus) may be noted. A weak suck reflex and consequent poor feeding occur in all infants with PWS.

For the remainder of the neonatal period hypotonia and associated morbidities continue to be the number one major medical concern. Failure-to-thrive is a common diagnosis, often leading to valiant efforts to increase body weight gain. However, it should be noted that obesity, defined as increased body fat relative to lean mass, is present even in these underweight infants with PWS<sup>68</sup>; feeding maneuvers may improve weight gain, while doing little to improve mass and function. However, severe undernutrition may have detrimental effects on bone growth and brain development.

Neuromotor and speech delay, the latter probably due to a combination of oromotor hypotonia and central cognitive defects, are also first noted in the neonatal period. Apnea and hypoventilation may be observed in the neonatal period and are nearly universal on formal testing.

The toddler/childhood stage has a markedly late beginning in children with PWS, with most children unable to ambulate until after 2 years of age. Although markedly decreased muscle mass and hypotonia continue during this period, the available muscle fibers gain sufficient function to enable food gathering and oromotor function, greatly



increasing the risk for overweight. Problems with apnea and hypoventilation may appear to abate during this period. Scoliosis may progress with ambulation and linear growth. Physical therapy can markedly improve physical function during childhood, although hypotonia is still evident.

One of the paradoxes of childhood growth in PWS is that linear growth will often decelerate as weight gain accelerates, typically beginning at 1 to 3 years of age. The major exceptions are those children who develop premature adrenarche. As discussed in a later section, these children can appear to have normal or accelerated linear growth; however, their final adult height is often severely compromised due to premature epiphyseal closure.

Adolescence is marked by incomplete sexual maturation. Adrenarche is usually normal or early, but male individuals with PWS rarely progress past mid-puberty and girls often fail to have menarche. Because of the hypogonadism and deficiencies in the growth hormone system, the usual pubertal growth spurt is blunted. Scoliosis, if present, can become particularly problematic starting in late childhood. Overweight also tends to progress rapidly, accompanied by increased risks for associated morbidities, such as diabetes mellitus. Unlike with usual exogenous obesity, bone mineral density is often low in adolescents with PWS, a problem that tends to progress through adult life.

The natural medical history of adults with PWS is relatively unstudied. Although most young adults with PWS are capable of living a semi-independent life, significant physical disability is evident. The combination of overweight and hypotonia eventually leads to wheelchair-dependence in many cases and respiratory insufficiency in most cases. In addition, osteoporosis, often caused or accentuated by untreated hormonal deficiencies, and scoliosis can also lead to significant morbidity.

## Mortality

The natural life span of individuals with PWS is currently undefined. Experience suggests that survival past the 5th or 6th decade is unusual. For instance, in a survey of 232 adults with PWS, the oldest was 62 years.<sup>78</sup> Perhaps because of the obvious feature of overweight and obesity, an anecdotal assumption has been made that many, if not most, individuals with PWS succumb to cardiovascular complications related to obesity. However, available data suggest that this may not be the case. As reviewed in other sections, insulin resistance does not appear to occur in the majority of adults with PWS. Atherogenic lipid profiles have also not been observed with increased frequency, and atherosclerotic heart disease has not been reported. Personal experience and recent data indicate that the major cause of overall mortality in PWS is respiratory insufficiency or cardiorespiratory failure. In many cases, demise appears to be triggered by acute or chronic pulmonary infection. It appears likely that underlying poor respiratory effort due to hypotonia may be a major contributing factor. This anecdotal impression is supported by available published reviews of cases.

In an early review of cases, Laurance et al.<sup>125</sup> found 24 individuals with PWS alive after age 15 years (15–41 years of age) and 9 deaths; 4 deaths occurred before age 15, and 5 between 17 and 23 years of age. Cardiorespiratory failure was the proximate cause of death in these cases.

A population-based survey in England included 66 individuals with PWS, aged birth to 46 years; 25% were found to have Type 2 diabetes mellitus, and 50% had recurrent respiratory infections.<sup>31,242</sup> Other morbidities included ulcers of the lower extremities (22% of adults), scoliosis (15% in children), and sleep disorders (20%). Limited data from this study indicated an extrapolated lifetime mortality rate of >3% per year.

An international review of mortality in PWS found 13 deaths in individuals under the age of 5 years and 14 deaths in individuals older than 9 years.<sup>185</sup> Of the 13 deaths in younger individuals, 9 were due to respiratory failure and 2 were judged to be “sudden” following onset of gastrointestinal symptoms and fever. In the 14 older patients, pneumonia was contributory in 3 cases and cardiorespiratory failure in 1. Of the other deaths, two were thought to be due to gastric dilatation, two had uncertain cause, and there were single cases of myocardial infarction, stroke, familial cardiomyopathy, femoral thrombosis, spinal myelitis, and malignancy. Nine of the younger and only three of the older patients were autopsied.

In a study of 36 adults with PWS in Australia, there were 10 deaths at a mean age of 33 years (range 20–49 years); 3 were due to pneumonia or cardiorespiratory arrest, 1 was due to respiratory illness complicated by congestive heart failure, 2 were undetermined, and there were single cases of hypoglycemia, myocardial infarction, stroke, and pulmonary embolus.<sup>193</sup>

A population-based study in Flanders of all patients diagnosed by DNA methylation analysis found no individuals with PWS over age 56 years and a marked drop in numbers of cases with age, particularly after age 32 years.<sup>229</sup> Seven cases of death were reviewed: three children succumbed to pneumonia and respiratory failure and four adults died from various causes—respiratory infection, cardiorespiratory failure, stroke, and car accident. Respiratory problems were thought to be possibly contributory in five of eight deaths (5 months to 43 years of age).<sup>200</sup>

Small adrenal size was identified in three of four autopsied patients in this latter series but was not reported in another series of seven autopsies.<sup>185</sup> The possibility of adrenal hypofunction at the time of death is unresolved, although other studies have shown normal adrenal function in PWS.

## Medical Concerns

Numerous medical conditions have been associated with PWS, with varying degrees of published documentation. For the purposes of discussion, PWS-associated physiology, pathophysiology, and medical morbidities will be grouped as follows:

*This Chapter: Medical Considerations*

- I. Disorders of Sexual Development and Maturation
  - A. Genital hypoplasia and cryptorchidism
  - B. Hypogonadism
- II. Musculoskeletal Disorders
  - A. Hypotonia
  - B. Scoliosis
  - C. Osteoporosis
- III. Respiratory and Circulatory Disorders
  - A. Respiratory disorders
  - B. Cardiovascular and cerebrovascular systems
- IV. Miscellaneous Medical Concerns
  - A. Thermoregulatory disorders, autonomic dysfunction, and anesthesia risk
  - B. Ophthalmologic disorders
  - C. Sensory function
  - D. Mitochondrial DNA
  - E. Epilepsy
  - F. Cancer
  - G. Infection

*Chapter 6: Gastrointestinal System, Obesity, and Body Composition*

- I. Gastrointestinal System and Disorders
  - A. Oropharynx
    - 1. Salivation
    - 2. Feeding and swallowing
  - B. Stomach
    - 1. Mechanical function
    - 2. Digestion
  - C. Intestines
  - D. Pancreas and liver
- II. Obesity and Nutrition
  - A. Overweight and obesity
    - 1. Diagnosis
    - 2. Pathogenesis:
      - a. Overweight and body composition
      - b. Energy expenditure
    - 3. Associated morbidities
  - B. Treatment
    - 1. Nutritional strategies
    - 2. Special nutritional considerations
    - 3. Associated morbidities
- III. Measurement of Body Composition
  - A. Review of methodologies
  - B. Summary comments

*Chapter 7: Growth Hormone*

- I. Background
- II. Growth hormone treatment
  - A. Efficacy of treatment in children with PWS
  - B. GH treatment of adults with PWS
  - C. Adverse effects
- III. Summary and Conclusions

Based on clinical experience and published studies, conditions that do not occur with increased frequency in PWS include the following:

1. Thyroid dysfunction<sup>1,29,36,51,126,177,206,240</sup>
2. Hyper- or hypoprolactinemia<sup>36,126,160,177,195,206</sup>
3. Adrenocortical dysfunction<sup>29,35,126,195</sup>
4. Abnormal melatonin secretion<sup>177</sup>
5. Parathyroid hormone disorders
6. Intrinsic defects in calcium or vitamin D metabolism (although nutritional deficits can occur)
7. Dyslipidemia<sup>22,170,204</sup>
8. Type 1 diabetes mellitus
9. Autoimmune or immunodeficiency disorders
10. Disorder of the renin/aldosterone/angiotensin<sup>29</sup> and antidiuretic hormone systems
11. Renal and hepatic disorders
12. Primary lung diseases, including asthma
13. Disorders of olfaction and taste<sup>72,171</sup> (not including food preference)
14. Hearing disorders (Auditory and visual processing disorders have been reported.<sup>199</sup>)
15. Slipped capital femoral epiphysis<sup>241</sup>
16. Seizure disorders

## Disorders of Sexual Development and Maturation

### Genital Hypoplasia and Cryptorchidism

#### *Pathophysiology*

Genital hypoplasia is a frequent finding in neonates with PWS, occurring in 13 of 15 cases (86.5%) reviewed for derivation of infant diagnostic criteria.<sup>44,105</sup>

In male infants with PWS, cryptorchidism is reported in >90% of cases; most cases are bilateral.<sup>17,54,57</sup> In comparison, cryptorchidism occurs in 5% or less of non-PWS infant males.<sup>19</sup> It is clinically important to distinguish true cryptorchidism from retractile and gliding testes,<sup>19</sup> although the evaluation and treatment of these conditions is similar. Small testes and scrotal hypoplasia, although usually not a true bifid scrotum, are also reported in most cases of PWS,<sup>53</sup> whereas micropenis is reported in less than 50%. Hypospadias and retention of female

structures have not been reported. Prostate and ductal systems have not been fully characterized, although anecdotal reports indicate that the testicular accessory structures are often noted to be hypoplastic at surgery. Inguinal hernia can be expected to occur in >90% of cases of cryptorchidism due to persistence of a patent processus vaginalis<sup>128</sup>; however, data in PWS regarding inguinal hernia risk is lacking.

Genital abnormalities in female infants with PWS have been more difficult to characterize, although neonatal labial hypoplasia has been reported.<sup>40</sup> Hypoplasia of the clitoris and/or labia minora was noted in 32 of 42 females with PWS (76%) evaluated at a mean age of 17.5 years. Internal female genital anatomy has not been characterized, although no specific abnormalities of müllerian duct derivatives have been described. In addition, no cases of inappropriate virilization or appearance of male structures has been reported.

Clues to possible mechanisms for the fetal genital malformations in PWS can be gleaned from the nature of the observed abnormalities and knowledge of normal fetal genital maturation, which has been extensively reviewed in the literature<sup>7,144,191</sup> and is only briefly summarized here.

In the male fetus, the first evidence for sexual differentiation, the appearance of the seminiferous cords and Sertoli cells, occurs at ~6–7 weeks gestation. Leydig cell production of testosterone is first detectable before 9 weeks gestation. Müllerian (female) duct regression occurs between 7 and 10 weeks, overlapping with Wolffian (male) duct differentiation between 8 and 12 weeks.

For the male external genitalia, elongation of the genital tubercle is noted by 8 weeks. By 16 weeks gestation, urethral closure with penile formation and fusion of the labioscrotal folds are complete. All of these events, and the formation of the prostate, are dependent upon the production of testosterone by the fetal Leydig cells and conversion to dihydrotestosterone, via the action of 5 $\alpha$ -reductase Type II in the target tissues. The external genitalia experience further growth and less significant differentiation after approximately 13 to 14 weeks gestation.

The testes originate at 7 to 8 weeks gestation in proximity to the inguinum and kidneys and are apparently anchored in place by the gubernaculum, a gelatinous structure that attaches the lower pole of each testis to the inguinal region. Testicular descent has been divided into two stages.<sup>110</sup> The first stage, occurring at 8–15 weeks gestation and sometimes termed transabdominal descent, involves cranial migration of the kidneys and other structures while the testes remain in place. The gubernaculum enlarges in an androgen-independent process that may be facilitated by testicular production of insulin-3 (also known as descandin), creating a path in the inguinal canal for future testicular descent. The inguinal canal is formed by differentiation of musculature surrounding the gubernaculum. During the second stage, at 28 to 35 weeks, the patent processus vaginalis protrudes through the internal inguinal ring, thereby transmitting intra-abdominal pressure to the gubernaculum.<sup>109</sup> This is thought to cause movement of the gubernaculum through the inguinal canal into the scrotum, thereby guiding initial testicular descent. As summarized by Hussman and Levy,<sup>109</sup> descent of

the testes is dependent on both gubernaculum-dependent development of the inguinal canal and on the sporadic increases in intra-abdominal pressure induced by fetal respirations and hiccupping. After descent, the gubernaculum regresses through an androgen-dependent mechanism. Androgens may also influence development of musculature involved in formation of the inguinal canal and optimization of intra-abdominal pressure.

Although fetal gonadotropin production is evident by 9 to 10 weeks, the early stages of testicular differentiation, androgen production, and genital development are likely maintained by placental chorionic gonadotropin, which is the predominant fetal gonadotropin through gestation. However, during late gestation, production of LH and possibly other fetal pituitary hormones appears to be necessary for completion of external genital development, genital growth and testicular descent, as evidenced by the common findings of micropenis and cryptorchidism in cases of congenital hypopituitarism (non-PWS).

It is important to realize that each stage of male fetal sexual differentiation and development is controlled by time-limited processes that are determined not only by hormonal exposure, but also by specific genes with time-limited activity.<sup>7</sup> Therefore, each step described above must occur within a specific "window of opportunity." In addition, the testicular hormones (insulin-3, testosterone) involved in testicular descent are largely active on a local or paracrine, rather than systemic, level. Therefore, unilateral defects in hormone action may lead to unilateral cryptorchidism.

In consideration of this knowledge of male genital embryology, a tentative theory for the occurrence of male genital abnormalities in PWS can be generated. Steps that are not abnormal in PWS include urethral closure and labioscrotal fusion, implying normal testicular differentiation, normal *in utero* testosterone production, and normal activity of 5 $\alpha$ -reductase through 16 weeks gestation. In addition, the usual location of undescended testes near the inguinal ring or in the inguinal canal in PWS-associated cryptorchidism implies normal androgen-independent transabdominal descent at 8–15 weeks. The preponderance of bilateral cryptorchidism indicates that unilateral testicular malfunction or structural abnormality is not involved. Finally, the not uncommon occurrence of bilaterally descended testes and the relatively low occurrence of micropenis suggest that the genital abnormalities are not intrinsic to the genetic defect per se, but may be secondary to other factors that occur with variable severity from one affected individual to another. Two major possibilities along these lines are (1) fetal gonadotropin deficiency, leading to decreased late-gestational testosterone deficiency; and (2) fetal hypotonia, leading to inadequate intra-abdominal pressure. Since both hypotonia and a variable, non-absolute gonadotropin deficiency occur in postnatal life, it appears likely that both factors are involved in the etiology of the male genital abnormalities in PWS.

Normal female external genital development has been characterized by Ammini et al.<sup>9</sup> The labial folds, clitoris and vestibule with single perineal opening are evident by 11 weeks gestation. Between 11 and 20



weeks, the labia majora, derived from the genital swellings (scrotal anlage in the male), continue to enlarge. However, the labia minora, derived from the genital folds (~penile shaft in the male), and the clitoris, derived from the genital tubercles (~glans penis in the male), show little change during this period. At 23–25 weeks, the labia minora enlarge and protrude past the labia majora, and the dual openings (urethra and vagina) move to the perineum. Thereafter, the labia majora become more prominent. Fetal pituitary gonadotropin levels peak at 20–24 weeks (FSH > LH) in the female, and a maximal number of ovarian primordial follicles are observed at 22–24 weeks, possibly stimulated by the FSH peak. In females with PWS, the major external genital abnormality has been noted to be hypoplastic labia minora and a small clitoris, structures that show maximal growth immediately following the fetal gonadotropin surge. Therefore, it appears likely that, as with males with PWS, the external genital abnormalities in some female infants with PWS may be related to a deficiency of fetal gonadotropin secretion.

### *Evaluation*

Any male neonate with unexplained hypotonia and cryptorchidism with or without micropenis should be suspected of having PWS, especially if there are no other anogenital abnormalities. Unexplained neonatal hypotonia is, of course, a stand-alone criterion for consideration of PWS testing<sup>80</sup>; however, cases of late-diagnosed (older children and adults) PWS presenting with hypotonia and cryptorchidism have been anecdotally observed by the authors. Similarly, in females with hypotonia, the presence of hypoplasia of the labia minora and/or small clitoris should further encourage consideration of testing for PWS.

In cases of cryptorchidism, evaluation for presence of testes and testicular function may be advisable before and after surgical treatment. Consultation with a pediatric urologist and pediatric endocrinologist is highly advisable. If the testicle(s) is completely nonpalpable, an initial inguinal/pelvic ultrasound should be performed. In some cases, a magnetic resonance imaging (MRI) may provide additional information,<sup>58</sup> although this procedure has not usually been necessary in our experience. Brain imaging studies are not particularly useful unless there is other evidence for pituitary or CNS dysfunction; intrinsic structural abnormalities of the central nervous system visible on routine imaging have not been identified in PWS.<sup>35,201</sup>

Single measurements of testosterone, LH, and FSH in the first few days of life or during the expected secondary gonadotropin surge at 30–60 days of age may, if positive, confirm the presence of functional testicular tissue. A testosterone level >20–50 ng/dL (700–1750 pmol/L) is indicative of testosterone production. However, although this random sampling is often useful in non-PWS infants with cryptorchidism, utility may be limited in congenital hypogonadotropic hypogonadism since gonadotropin priming may be necessary for optimal testicular response. Therefore, a negligible random neonatal testosterone level in an infant with PWS does not preclude the existence of functional testicular tissue.

Gonadal stimulation testing to document functional testicular tissue is not usually required, but may be indicated in those patients with true bilateral cryptorchidism and a low random neonatal testosterone level or in older infants/children where the hypothalamic-pituitary-gonadal axis may be expected to be naturally suppressed. Since orchiopexy is usually not performed in the immediate neonatal period, such testing can often be delayed until immediately prior to surgery. A standard "short" testosterone stimulation test involves daily intramuscular injections of chorionic gonadotropin ( $1500 \text{ U/m}^2/\text{dose}$ ) for 3 to 5 days, with serum testosterone measured at baseline and 24 hours after the final injection. However, since gonadotropin priming may be necessary to achieve testicular secretion, a "long" test may be preferable. A typical regimen is chorionic gonadotropin 500–1000 U by intramuscular injection twice a week (e.g., Monday/Thursday) for 5 weeks (10 doses total) with baseline and 24-hour post-final-dose serum testosterone levels. The baseline level is theoretically not necessary for either the short or long test, although it may provide information about basal secretion and tissue responsiveness. A post-test testosterone level of  $>100\text{--}200 \text{ ng/dL}$  is clearly indicative of testicular activity; levels between  $20 \text{ ng/dL}$  and  $100 \text{ ng/dL}$  are considered equivocal, although there is presumably some amount of functional tissue present. The long test has the additional theoretical advantages of more prolonged testosterone production, possibly resulting in some penile growth, testicular enlargement, and possible testicular descent. However, these latter effects are rarely, if ever, observed in PWS. Intranasal and subcutaneous gonadotropin administration have also been used for diagnosis and treatment of cryptorchidism; however, reports specific to PWS are limited.<sup>91,112</sup>

### ***Treatment***

*Micropenis:* In the male infant with PWS and micropenis, a short course of low-dose testosterone may be used to improve the appearance and function of the penis.<sup>84</sup> It is often stated that a stretched penile length of  $<1.5\text{--}2.0 \text{ cm}$  could lead to difficulty with toilet training and upright urination, as well as complicate peer relationships<sup>40</sup>; however, scientific data relating to these effects is lacking. Treatment of micropenis in infancy is often based on the judgment of the physicians and parents. In non-PWS individuals, there is no evidence that such treatment adversely affects later penile growth potential.<sup>23</sup>

If treatment is elected, a typical treatment regimen is depot testosterone (enanthate or cypionate),  $25 \text{ mg}$  by intramuscular injection every 3 to 4 weeks for 3 to 6 months. A longer course or higher dose is not recommended since either of these could lead to inappropriate virilization and acceleration of skeletal maturation. Experience suggests that this treatment should be initiated in infancy, preferably before 6 months of age, for maximal effectiveness. There is a theoretical risk for triggering central puberty in older children, although this risk may be minimal in children with PWS. The child should be examined prior to each dose to gauge clinical response and the necessity for additional doses; a stretched penile length  $\geq 2.0 \text{ cm}$  is adequate. Particularly in the obese child, the suprapubic fat pad should be fully compressed when obtain-

ing a penile length measurement. On occasion, a few strands of pubic hair and acceleration of linear growth may be observed during the treatment course, but these effects invariably abate within a few weeks after treatment is completed.

*Cryptorchidism:* Spontaneous descent of a cryptorchid testicle(s) may occur in a prepubertal or pubertal boy with PWS,<sup>88</sup> as it does in a significant proportion of cases of non-PWS cryptorchidism.<sup>19</sup> The converse condition, spontaneous ascent of a descended testicle(s) has not been reported in PWS. In other cases, medical intervention with gonadotropin administration may be successful in achieving testicular descent,<sup>214</sup> although the ultimate success rate of hormonal therapy is low in non-PWS cases of true cryptorchidism<sup>207</sup> and data in PWS is lacking.

In both PWS and non-PWS cases of cryptorchidism, the justification for and timing of surgical exploration and orchiopexy have been controversial. Studies in non-PWS populations indicate that cryptorchidism is associated with a 35- to 48-fold increased risk for testicular cancer.<sup>128</sup> However, it is unclear whether surgical correction of cryptorchidism (orchiopexy) reduces the risk for cancer. Several studies indicate that the risk for testicular cancer is negligible if surgical correction is performed before puberty, whereas the risk for cancer is increased >30-fold thereafter.<sup>99</sup> The majority of such tumors in non-PWS cryptorchid males are testicular carcinoma, although germ cell and Sertoli cell tumors are also reported.<sup>50</sup> Given these statistics, it may be somewhat surprising that only two cases of testicular cancer in PWS have been published, a seminoma in a 40-year-old man<sup>178</sup> and a germ cell neoplasm in a 9-year-old boy with cryptorchidism.<sup>111</sup> Since the risks for maldescent-associated cancer in non-PWS cases may also involve an association with puberty, it is possible that the numbers of observed cases in PWS are low due to early correction and lack of later spontaneous pubertal development.

Facilitation of physical surveillance for torsion and testicular tumors has also been proposed as a justification for orchiopexy.<sup>128</sup> In one study of non-PWS individuals, more than half the cases of torsion of an intra-abdominal testis, usually presenting with pain and discomfort, were associated with germ cell tumor.<sup>176</sup> In PWS, a single case of germ cell neoplasia discovered in a cryptorchid testicle has been reported.<sup>111</sup>

Preservation of testicular function and fertility has been given as another reason for treatment of cryptorchidism. In a study of 1,335 non-PWS boys with cryptorchidism, an increased risk for germ cell absence was noted after 15–18 months of age, and this was associated with adult infertility in a follow-up study, while surgical correction prior to this time appeared to preserve fertility.<sup>50</sup> This may have relevance to PWS, in which lack of germ cells has been found on testicular biopsy.<sup>29,116,235</sup> Preservation of male fertility has not been an emphasis in the treatment of PWS, but the evolving treatment of this condition may soon justify consideration of this possibility.

Among other factors to be considered, an undescended testis located in the inguinum may be at increased risk for traumatic injury. In non-PWS cases, cryptorchidism is associated with a >90% chance for a

patent processus vaginalis and consequent increased risk for hernia and hydrocele,<sup>128</sup> thus providing another justification for surgical evaluation and repair. Cosmetic and psychosocial considerations may also be important in some cases.

All cases of cryptorchidism should be evaluated by an experienced pediatric urologist before 6 months of age. Since infants with PWS may present unique surgical and anesthesia risks, surgical procedures may be delayed and medical therapy initially attempted. Orchiopexy may be particularly difficult in PWS due to the degree of maldescent and hypoplastic accessory structures. Either before or after surgery, the testicles may be atretic and nonfunctional, and experience suggests that the risk for post-orchiopey testicular retraction and degeneration is high. In some cases, removal of the testicular tissue with or without placement of prostheses may be a preferred or necessary option.

## Hypogonadism

### *Pathophysiology*

Hypogonadism, evidenced by incomplete pubertal (sexual) development occurs in more than 80% of adolescents and adults with PWS.<sup>105</sup> Puberty normally occurs as a two-system process, beginning after 8 years of age: adrenarche and gonadal maturation, or gonadarche. Adrenarche involves production of adrenal androgens, resulting in secondary sexual hair growth (pubic and axillary hair); this effect is superseded in males by testicular production of testosterone. The control of adrenarche is not completely defined. In boys, gonadarche involves testicular production of testosterone, resulting in masculinization. In girls, gonadarche includes ovarian maturation and estrogenization. Gonadarche is controlled by pituitary production of the gonadotropins, luteinizing hormone (LH), and follicle-stimulating hormone (FSH), which are in turn controlled by hypothalamic production of gonadotropin-releasing hormone (GnRH).

In PWS, adrenarche usually occurs normally in both sexes, although a relative decrease in secondary sexual hair has been anecdotally reported. A significant proportion of children with PWS have premature adrenarche, perhaps related to insulin resistance or decreased insulin sensitivity<sup>122,182,184</sup> (discussed further in Chapter 6).

On the other hand, gonadarche is usually abnormal in PWS. Many female patients with PWS progress through phenotypic puberty (breast development) but fail to have normal menstrual cycles and/or have early menopause. Breast development can progress to full maturation, although 49 of 81 individuals (64%) in a survey study were reported to have small or flat breasts.<sup>78</sup> Breast development is presumably due to estrogens originating from the ovaries and/or peripheral conversion of adrenal precursors; estrogen receptor variants have not been identified in PWS. Virtually all males with PWS have a failure to progress past mid-puberty.

It is likely that the postnatal hypogonadism in PWS is a continuation of hypogonadotropic hypogonadism that begins *in utero*. However, there are virtually no data regarding gonadotropin secretion in infants or pre-teen children with PWS. It is not known, for instance, whether

the normal postnatal rise in FSH and LH secretion occurs in infants with PWS. Although gonadotropin response to exogenous GnRH may be absent or low in preteen children with PWS,<sup>251</sup> this may be considered a typical pre-pubertal pattern in non-PWS children and not necessarily indicative of pathology.

In adolescents and adults with PWS, low baseline and GnRH-stimulated gonadotropin levels are a frequently reported finding, arguing for an intrinsic hypogonadotropic hypogonadism, i.e., at the hypothalamic or pituitary level. Primary gonadal failure has not been reported, except in cases of acquired testicular atrophy,<sup>186</sup> and there is a single report of abnormal ovarian histology in PWS.<sup>29</sup> In addition, treatment with gonadotropin or gonadotropin-releasing hormone can result in improvement or normalization of gonadal function,<sup>29,91</sup> implying that gonadal steroidogenesis is not a primary disorder.

On the other hand, multiple observations indicate that irreversible, complete intrinsic gonadotropin deficiency at the pituitary or hypothalamic level may not be involved. Normal or precocious spontaneous menses have been reported,<sup>29,40,117,232</sup> implying cyclic production of gonadotropins. In addition, elevated gonadotropin secretion has been observed in some cases, especially following primary gonadal failure (i.e., with castration or testicular atrophy),<sup>150,186,188,245</sup> and some individuals with PWS have apparently normal gonadotropin responses on stimulation testing.<sup>177</sup>

Clomiphene citrate, a triphenylethylene estrogen antagonist, has been observed to stimulate gonadotropin secretion and gonadal function (including menses and spermatogenesis) in males and females with PWS.<sup>29,88,130,141</sup> In non-PWS individuals, clomiphene is commonly used for induction of gonadotropin secretion and ovulation during treatment of female infertility. As an estrogen analog, clomiphene binds to intracellular estrogen receptors in the arcuate nucleus of the hypothalamus, thereby blocking estrogen inhibition of gonadotropin-releasing hormone (GnRH) secretion, resulting in stimulation of pituitary gonadotropin secretion.<sup>62</sup> Clomiphene also appears to sensitize the pituitary gland to GnRH action, but direct effects of clomiphene to stimulate pituitary gonadotropin secretion have not been found. Finally, clomiphene may also sensitize the ovary to gonadotropin action. Therefore, clomiphene stimulation of gonadotropin secretion and action in individuals with PWS argues against an intrinsic or complete hypothalamic or pituitary GnRH or gonadotropin defect.

Induction of menses in PWS has also reported with use of fluoxetine (Prozac),<sup>236</sup> a selective serotonin reuptake inhibitor (SSRI) not uncommonly used for psychopharmacologic treatment of PWS. Induction of menses has been reported in a 25-year-old woman with PWS during treatment with citalopram (Celexa), another SSRI<sup>8</sup>; this patient subsequently became pregnant after withdrawal of citalopram, although her menses had become "sparse." SSRIs are thought to act by inhibiting neuronal reuptake and metabolism of serotonin (5-hydroxytryptamine, 5-HT), thereby increasing the local concentration and activity of serotonin. Serotonin-secreting neurons originate primarily in the midbrain and extend throughout the central nervous system. The role of sero-

tonin in gonadotropin secretion has not been completely defined; however, it appears to modulate pulsatile secretion of FSH (but perhaps not LH) by affecting pulsatile hypothalamic GnRH secretion.<sup>169,215,227</sup> Therefore, these cases provide additional arguments against an intrinsic complete GnRH/gonadotropin deficiency in PWS.

A possible mechanism for partial, variable deficiency in gonadotropin secretion in PWS is suggested by rodent studies in which disruption of *Ndn*, an imprinted gene located within the PWS region that codes for neocdin (neurally differentiated embryonal carcinoma-cell derived factor), results in a 25% reduction in GnRH neurons in the hypothalamus.<sup>149</sup> However, corollary studies in humans have not been reported.

Male fertility has not been reported in PWS and testicular biopsy has been reported to show Sertoli cell-only histology<sup>29,116,235</sup>—i.e., presence of Sertoli cells, which provide the milieu for spermatogenesis, and Leydig cells, which produce testosterone, but absence of germinal cells (spermatogonia). It is uncertain whether this is due to lack of LH stimulation of Leydig cell testosterone production (a requirement for spermatogenesis) or lack of FSH stimulation of Sertoli cell mitosis and/or some other factor(s). The reported induction of biopsy-confirmed spermatogenesis with clomiphene in a young adult with PWS<sup>88</sup> suggests that the abnormal histology is not due to an intrinsic testicular defect.

Fertility in PWS may also be limited by social factors. Most adults with PWS are not married and, presumably, have limited sexual contact. Social limitations to fertility may be altered as advances in medical and behavioral treatment improve physical outcomes and lifestyle choices.

### **Evaluation**

Adolescents with PWS will usually have hypogonadotropic hypogonadism, unless a primary gonadal defect is present. For research purposes or in equivocal cases, serum FSH and LH levels can be measured at timed intervals following intravenous administration of GnRH.<sup>250,251</sup> Clomiphene pretreatment may augment gonadotropin secretion.

In cases where testicular atrophy or necrosis is suspected, random simultaneous measurements of testosterone (in boys), FSH, and LH are usually sufficient; elevations of gonadotropins and low levels of testosterone can be expected if there is primary gonadal failure.<sup>150,186,188,245</sup> Primary ovarian failure has not been reported in PWS; however, elevated gonadotropin levels would be expected in such a case.

Measurements of serum testosterone may be useful in guiding hormone replacement therapy in males. Estrogen (estradiol) measurements in females are less useful due to large inter- and intra-individual temporal variability as well as limited assay sensitivity.

Fertility testing is rarely, if ever, clinically warranted in PWS. Despite the obesity, there does not appear to be an increased occurrence of polycystic ovary syndrome in PWS.

### **Treatment**

Virtually all males with PWS fail to progress past mid-puberty and testosterone levels are usually low relative to the adult normal range.



However, androgen replacement therapy has been somewhat controversial, primarily due to anecdotal concerns that testosterone treatment might cause inappropriately aggressive behavior or worsen other behavioral problems, although there are no published data showing such a relationship. On the other hand, testosterone therapy, combined with psychotherapy, was reported to improve behavior in an adolescent with PWS.<sup>212</sup> In addition, detailed studies in non-PWS eugonadal and hypogonadal men have not shown an effect of physiologic or moderately supraphysiologic levels on measures of aggression.<sup>159</sup> Our experience suggests that testosterone replacement should be started at a biologically appropriate time, i.e., in early adolescence; late initiation of therapy may be associated with adverse psychosocial outcome, perhaps due to an impact on the socialization process.

Normal adult testosterone levels are considered to be necessary for preservation of bone mass and prevention of osteoporosis in males.<sup>218</sup> In addition, testosterone has positive effects on muscle mass and strength in hypogonadal men.<sup>21</sup> Since osteoporosis and hypotonia are major causes of morbidity in PWS, replacement therapy would appear to be medically advisable.

In recent years, new delivery systems for testosterone replacement have become available.<sup>21</sup> The traditional intramuscular injection of 200 mg depot testosterone once or twice monthly may no longer be preferred in most cases since this causes an acute supraphysiologic rise over 24 hours, followed by a steep decline to subnormal levels over 2 to 3 weeks. If supraphysiologic levels of testosterone have even minor effects on mood and behavior, then the depot injection may cause inappropriate swings in these parameters. Testosterone patches are now available at several dose levels. The patches are changed daily, can be applied to any skin area (the back, thighs and buttocks are particularly convenient), and the 5-mg patch usually achieves low-normal adult testosterone levels. Anecdotal experience indicates that pruritis and skin picking at the patch site have not been a problem, even in patients who have skin picking in other areas. Finally, testosterone gel preparations can be useful in selected cases, although precautions must be taken to avoid cross-contamination of adult females and prepubertal children.

Estrogen replacement therapy, usually combined with progestin, is an established therapy for non-PWS hypogonadal women. This treatment has been shown to have multiple benefits, including preservation of bone mass and reduction of fracture risk. However, estrogen replacement in women with PWS is not as well established. Most women with PWS have evidence of estrogen effect (breast development) and menses are not uncommonly reported. Osteoporosis is a documented morbidity in adult women with PWS; however, there are no published data showing efficacy of estrogen replacement. Nevertheless, estrogen replacement may be advisable in women with PWS, particularly in the presence of amenorrhea or oligomenorrhea and/or osteoporosis.

Hypogonadism in women can be treated with any of a number of approved oral or transdermal forms of estrogen in combination with progestins or micronized progesterone. Commercial birth control

preparations are often used for convenience, are anecdotally well tolerated, and are probably the most commonly prescribed modality in our experience. However, in view of the low reported resting energy expenditure and predisposition for adiposity of Prader-Willi syndrome patients and the report of divergent effects of oral vs. transdermal estrogen on lipid oxidation and fat accumulation,<sup>162</sup> it could be argued that non-oral forms of estrogen might be physiologically preferable in this population. In addition, in consideration of the increasing use of growth hormone therapy in PWS, the growth hormone replacement dose required for comparable response in growth hormone deficient non-PWS women taking oral estrogen was more than double that of women on transdermal estrogen.<sup>49</sup> Thus, treatment with transdermal estrogen with oral progestin (to reduce endometrial cancer risk) or a combined estrogen-progestin patch may be preferred, although there is limited experience and no published data using these preparations in PWS.

Testosterone or estrogen replacement therapy should be coupled with careful monitoring of clinical and behavioral status, and bone mineral density. Testosterone levels may be useful in adjusting the patch or gel dose. Monitoring of other biochemical parameters (coagulation profiles, liver enzymes, prostate-specific antigen) may be advisable in some cases. Prostate or gynecologic examinations should also be considered, as appropriate.

In either males or females with PWS who are unable to tolerate gonadal steroid replacement, bisphosphonate therapy can be considered for treatment or prevention of osteoporosis, as has been recommended for similar situations in non-PWS women.<sup>154</sup> Bisphosphonate treatment may also be used as an adjunct to gonadal steroid replacement in cases with severe osteoporosis.

Contraception per se is probably not necessary for most individuals with PWS, although it may be a consideration for women with menstrual cycles. However, sexual activity and risks for sexually-transmitted disease are a reality and concern in the treatment of PWS. Therefore, all adolescents and adults with PWS should receive appropriate education and counseling.

## Musculoskeletal Disorders

### Hypotonia

Hypotonia is a universal feature of PWS, manifesting in fetal life as hypomotility and continuing through postnatal existence. Neonatal hypotonia is considered to be the key criterion for clinical suspicion of PWS in neonates.<sup>77,80,105,209</sup> The proximate etiology of the hypotonia is decreased muscle mass, but the pathogenesis of this condition is unknown. Neuromuscular studies, including electromyography and nerve conduction velocity studies, are usually normal; this feature of hypotonia with normal neuromuscular studies was included in the clinical diagnostic criteria.<sup>105</sup> Ultrasound analysis showed no abnormality in muscle echogenicity in eight infants with PWS (9 days to 18

months old). A few autopsied cases showed cerebellar changes that could cause motor dysfunction<sup>94,95</sup>; however, these findings do not explain the decreased muscle mass and related neuromuscular features.

Histologic and ultrastructural studies of muscle fibers in PWS are limited. No morphologic changes are identified on routine staining and microscopy and the fibers appear mature.<sup>5,196</sup> In one infant, there was a relative paucity of Type 1 fibers and a preponderance of small Type 2 fibers.<sup>14</sup> In a study of 11 PWS infant muscle biopsies, the Type 1 fibers showed increased size variability and nonspecific abnormalities of Type 2 fibers were noted.<sup>196</sup> However, examination of muscle fibers generally shows minimal, if any, abnormality.<sup>5,6,196</sup> Ultrastructural analysis in one case showed increased subsarcomeric accumulation of normal-appearing mitochondria and sarcomeric Z-line changes. The composite data from these limited studies appear to be more consistent with a peripheral muscular disorder or disuse than to a central nervous system myopathy. A possible contribution of a deficiency in insulin-like growth factor-I (IGF-I), a growth hormone-related growth factor, is suggested by the correlation of IGF-I levels with fat-free mass.<sup>217</sup>

Physical therapy is an essential element of treatment for Prader-Willi syndrome. However, data relating physical therapy and improvement in neuromuscular function in PWS are notably lacking. Due to the lack of muscle mass, both strength and endurance are deficient, and the range of innate activity can be quite variable.<sup>152</sup> The usual functional improvement in muscle function during infancy and childhood may be due to strengthening of existing muscle fibers rather than to significantly increased muscle mass per se. One study indicates that fat mass may be inversely correlated with physical activity levels in PWS<sup>217</sup>; a relationship of activity and fat-free mass was not reported. A 6-month aerobic exercise program (walking) led to significant improvement in aerobic capacity, coupled with decreased body fat and weight, in six adults with PWS as compared with a control group (n = 5).<sup>190</sup> A study using brief, daily calf muscle training (repetitive heel lowering on a household stair) in 17 children with PWS (aged 4.4–18.8 years) found a significant decrease in calf skinfold thickness and significant increases in calf circumference, physical activity, and endurance (physical capacity).<sup>69</sup> These data provide objective evidence that physical therapy can improve muscle mass and function in PWS.

Growth hormone treatment has also been shown to improve muscle strength and endurance in PWS. This topic is discussed in more detail in Chapter 7. Adrenarche and testosterone replacement therapy are subjectively associated with improved muscle function in some patients; however, objective data in PWS are not available.

## Scoliosis

Scoliosis, a commonly observed disorder in PWS, is defined as a lateral spinal curvature (Cobb's angle) of >10 degrees on standing radiograph.<sup>172</sup> Cases may be observed *in utero* and in the newborn period,

suggesting early initiation of pathogenetic mechanisms. However, experience indicates that most cases are diagnosed clinically in childhood, as with non-PWS scoliosis.<sup>172</sup> Notable progression occurs during late childhood and adolescence and continues into adult life, often exacerbated by osteoporosis. Laurance et al.<sup>125</sup> found scoliosis in 15 of 24 adults with PWS, 2 of whom received surgical treatment. A survey of PWS individuals in Italy showed 42 of 72 (59%) with scoliosis, including 12 of 16 deletion cases (75%).<sup>170</sup> A population survey in the U.K. found a 15% prevalence of "severe" scoliosis across all age groups.<sup>31</sup> In a survey study of 232 adults with PWS, nearly half reported scoliosis that was significant enough to require treatment.<sup>78</sup> Other reports estimate that >80% of individuals with PWS are affected.<sup>106</sup>

The pathogenesis of scoliosis in PWS is not defined but most likely falls into the category of neuromuscular scoliosis. Congenital or acquired primary vertebral abnormalities are not commonly observed, and other causes, such as trauma or degenerative disease, are also not likely. Although many cases of congenital scoliosis in PWS have been reported, there has been no association with cardiac, spinal cord, renal, or other malformations as occurs with idiopathic congenital scoliosis.<sup>15</sup> Scoliosis is often noted in PWS individuals who are not overweight,<sup>197</sup> indicating that weight is not a causative factor.

Neuromuscular scoliosis has been divided into neuropathic and myopathic subcategories.<sup>140</sup> Neuropathic scoliosis is associated with disorders of the upper or lower motor neurons (e.g., cerebral palsy and poliomyelitis, respectively). Myopathic scoliosis is associated with primary muscle disorders, such as congenital hypotonia and muscular dystrophy. Abnormal kyphosis or lordosis (posterior or anterior spinal angulation, respectively, as viewed from the side) is also frequently noted in neuromuscular scoliosis, as it is in PWS. Unlike the more common idiopathic adolescent scoliosis, neuromuscular scoliosis tends to progress through adult life, as observed with PWS scoliosis. Therefore, the described and anecdotal characteristics of scoliosis in PWS most closely resemble myopathic neuromuscular scoliosis, i.e., due to hypotonia of the paravertebral muscles.<sup>252</sup>

The risk for scoliotic curve progression increases with linear (height) growth in idiopathic adolescent scoliosis<sup>172</sup>; data on curve progression in PWS or other forms of neuromuscular scoliosis are lacking, although anecdotal information suggests a similar association. Back curvature should be carefully monitored during treatment with growth-promoting therapies, such as growth hormone and anabolic steroids.

The impact of scoliosis on health is not well defined in PWS. Back and lower extremity pain are frequent complaints in scoliotic individuals without PWS. However, experience indicates that these complaints are rarely encountered in those with PWS, even in cases with severely abnormal curvatures, possibly because of the known deficit in pain sensation.<sup>105</sup>

In infants without PWS, severe curves have been associated with respiratory compromise, but these degrees of curvature are not often observed in infants with PWS. Mild to moderate curvatures (>30 degrees) in adolescents and adults without PWS are thought to cause

inefficient coordination of respiratory muscle function and the thoracic cage, resulting in decreased maximal inspiratory and expiratory pressures and reduction in exercise capacity.<sup>121</sup> Compensatory mechanisms involve recruitment of thoracic and abdominal musculature, and this is likely to be deficient in the presence of hypotonia and decreased muscle mass, as is observed in PWS. In non-PWS scoliosis, respiratory symptomatology progressively increases with curves of >70 degrees, with significant risks for respiratory failure at >100 degrees. Experience suggests that a contribution to respiratory compromise is observed with lesser degrees of curvature in PWS; however, published data are lacking.

Excessive kyphosis or lordosis can also be a concern.<sup>134</sup> The normal back has a balanced thoracic kyphosis and lumbar lordosis. Extreme accentuation (hyperkyphosis) or extension of the kyphotic curve into the lumbar region can lead to spinal cord stretching, injury, and paraplegia in non-PWS individuals. Extreme lordosis can be associated with respiratory compromise. There are no published reports of kyphosis- or lordosis-related morbidities in PWS, although clinical experience indicates that these types of curvature abnormalities are not uncommon.<sup>82</sup>

Given the high rate of occurrence and the potential associated morbidities, all individuals with PWS should be regularly screened for abnormal back curvature. Some PWS experts have recommended spine radiographs at regular intervals for all patients with PWS, while others recommend regular clinical screening, with radiographs obtained only if indicated by abnormal findings. The Adams forward bending test is the standard clinical screening procedure for scoliosis, performed with the patient standing with his/her back to the observer and feet together, bending forward with knees flexed and arms extended (hanging). Abnormal spinal curvature, asymmetric elevation of one shoulder, and/or pelvic tilt should all be indications for further investigation. A similar examination with the patient standing upright, combined with examination of the gait, can also be a useful screening tool. A lateral examination should be performed to detect abnormal kyphotic and lordotic curves. Clinical detection of scoliosis in individuals with PWS may be hindered by obesity, hypotonia, and lack of cooperation; in such cases, radiographic screening may be indicated. Diagnosis is based on the standing radiograph, with anteroposterior (for scoliosis) and lateral (for kyphosis/lordosis) views.

Consultation with an experienced orthopedist is essential as soon as an abnormal curvature is identified, and the treatment plan should be carefully coordinated with other therapies. Treatment of scoliosis in PWS requires conscientious medical observation to determine appropriate timing of treatment: a spinal orthosis (brace) for mild to moderate curves and surgical intervention for severe, rapidly-progressing curves. While intermittent spine radiographs may or may not be indicated for routine screening, they are definitely a mainstay of monitoring for progression. In neuromuscular scoliosis, bracing is typically used to improve the functional position of the trunk and may permit delay of surgical procedures in a younger patient. In non-PWS patients,

progression of mild degrees of curvature associated with hypotonia can be slowed with bracing<sup>20</sup>; specific data in PWS are lacking.

Surgical stabilization of scoliosis can be difficult in PWS. Problems with rod fixation may be due to poor bone and tissue quality.<sup>82,173</sup> In addition, there can be significant morbidity due to respiratory compromise and infection. In a review of 33 cases of individuals with PWS treated with posterior spinal instrumentation (rod placement), excess bleeding (55%), soft bone (27%), fragile soft tissues (9%), sepsis (15%), and respiratory problems (15%) were the most commonly reported complications.<sup>113</sup> Growth hormone therapy has been anecdotally reported to improve surgical outcome, perhaps by improving bone and tissue quality and respiratory function.

Finally, there are limited data regarding efficacy of scoliosis therapy in PWS. In non-PWS individuals with scoliosis, surgical therapy can prevent respiratory compromise; however, similar therapy can be detrimental in cases where lung function is already impaired.<sup>121</sup>

### **Osteoporosis**

Osteoporosis has been defined as a “skeletal disorder characterized by compromised bone strength predisposing a person to an increased risk of fracture.”<sup>3,155</sup> Bone strength is dependent on both bone mineral and bone quality. However, since overall bone quality and strength are difficult to measure, bone mineral, which accounts for about two thirds of total bone strength, is commonly used to define osteoporosis.

A complete discussion of normal bone physiology is beyond the scope of this text. However, a few basic principles are essential to understanding bone pathology in PWS. Throughout life, there is continuous loss and gain of bone mineral. During childhood, there is progressive net accretion of bone matrix and subsequent mineralization. Bone mineral density, the amount of bone mineral per unit of bone mass, is relatively low in early life and gradually increases throughout childhood and adolescent growth. Peak bone mass is reached at completion of linear growth, and peak bone mineral density occurs in the third decade of life. Thereafter, there is progressive net loss of bone mineral.

Optimal net accretion of bone mass and mineralization during childhood and adolescence is dependent upon several factors, including hormones (growth hormone, gonadal steroids, vitamin D), nutrition (particularly calcium), and neuromuscular stimulation (exercise). Deficiencies in any of these areas could lead to inadequate bone mass accretion and osteoporosis, either in childhood/adolescence or later in life, as the normal loss of bone mineral occurs. Deficiencies of these factors after attainment of peak bone mass will lead to accelerated loss of bone mineral and osteoporosis. In addition, several factors may inhibit or reverse bone mineralization, including chronic use of glucocorticoids, chronic systemic illness, and immobility.

As discussed in other sections, individuals with PWS have low growth hormone, low gonadal steroid levels, and low neuromuscular activity. In addition, vitamin D levels may be low due to lack of sun



exposure, and there may be deficient intakes of both calcium and vitamin D for individuals on calorie-restricted diets. Therefore, it is not particularly surprising that low bone mineral has been frequently reported in PWS.<sup>27,33,41,108,127,223</sup> Biochemical markers of bone turnover may also be elevated,<sup>223</sup> as might be expected from the probable etiologies. On the other hand, there may be a protective effect(s) of weight, weight-bearing exercise, and/or body fat on bone mineralization,<sup>148,174</sup> although these have not been demonstrated in PWS. Anecdotal experience suggests that decreased bone mineral density in PWS is associated with increased fracture risk and, perhaps, abnormal progression of spinal curvature; there are no published data supporting these associations.

For many reasons, dual-energy X-ray absorptiometry (DXA) has become the standard diagnostic method for assessment of bone mineral density<sup>70</sup>; principles of this method are discussed in the next chapter. Most research related to osteoporosis has focused on women, since osteoporosis and fracture risk in postmenopausal women are major public and individual health concerns. Osteoporosis-related fragility fractures in this population are primarily located in the hip and lumbar spine. (A fragility fracture can be defined as a fracture that occurs during normal activity or minor trauma that would not normally cause a fracture in a healthy young adult.) Because of this, standards for diagnosis of osteoporosis are based on DXA analysis of bone mineral density in the femoral neck and the upper lumbar vertebrae (L1–4).

DXA facilities are readily available in most medical institutions. A DXA scan is noninvasive, painless, involves minimal radiation exposure (less than a chest X-ray) and takes only a few minutes. When ordered for assessment of bone mineral status (e.g., to diagnose or monitor osteoporosis), the report typically includes the measured bone mineral parameters and a T-score for the bone mineral density at the hip and spine. The T-score is the standard deviations from the average measurement for a healthy, young, white female at peak bone mass (the reference standard). Therefore, a lumbar T-score of  $-2.0$  means that the L1–4 bone mineral density is 2 standard deviations below the mean for a healthy young, white female. For adult women, fracture risk and definition of osteoporosis is based on the T-score for bone mineral density (or bone mineral content), as follows<sup>3</sup>:

Normal: T-score between  $-1$  and  $+1$

Osteopenia: T-score less than  $-1$  but greater than  $-2.5$

Osteoporosis: T-score less than  $-2.5$

Severe osteoporosis: T-score less than  $-2.5$  *and* one or more fragility fractures

It should be noted that osteopenia is not considered to be a disorder, and it is not currently defined as a risk factor for fragility fractures.

By definition, all children and adolescents can be expected to have a low T-score since peak bone mineralization has not been attained. Therefore, DXA measurements for children often refer to standard deviation (Z) scores, based on norms established by age, sex, and ethnicity,<sup>70</sup> using the same guidelines referred to for T-scores (osteoporosis

defined as Z-score less than  $-2.5$ ). Adult male standards are also not well defined and results are usually interpreted relative to the female T-score standard. However, fracture risk has not been defined for T- or Z-score levels in children or adult men.

Another caveat with DXA procedures is that results vary considerably according to instrumentation.<sup>70,124</sup> Technologies vary among manufacturers and direct comparisons of results are not feasible. Alternate sites (e.g., finger, ankle, heel) and alternate technologies, such as ultrasound bone density measurements, are also not directly comparable to traditional DXA results and may not be appropriately standardized in relation to age, sex, and fracture risk. Therefore, physicians should be careful to obtain sequential measurements using a single type of device (e.g., the same body regions measured using a device from the same manufacturer) if the intent is to compare results between procedures.

Although a relationship between bone mineral status and fracture risk has not been established for PWS, many specialists include DXA analyses in the routine care plan for individuals with PWS.<sup>127</sup> Because prevention of osteoporosis and fracture risk is more effective than secondary treatment, DXA screening should begin in childhood or early adolescence, during the period of bone accretion. Even in the presence of a normal DXA analysis, a repeat scan may be advisable if risk factors are present (e.g., hypogonadism, growth hormone deficiency, low activity) to assess the direction and rate of bone mineral changes.

Preventive treatment of low bone mineral density in PWS should include nutritional therapy (vitamin D and calcium supplementation, if needed), hormonal replacement (discussed in other sections of this chapter and in Chapter 7), and exercise. Caretakers should also be aware that individuals with PWS may have decreased deep pain sensation; therefore, bone fractures may not be accompanied by complaints of pain. Unusual gait, posture, or limb movements may signal a need for further investigation.

If there is inadequate accretion of bone mineral, excessive loss of bone mineral, or continuing osteoporosis with or without fragility fractures, bisphosphonate treatment may be advised, particularly for adolescents and adults. Typical regimens involve weekly oral doses of alendronate or risendronate, or monthly ibandronate. These medications must be administered on an empty stomach with water, with a sufficient subsequent interval before food intake to prevent reflux and esophageal complications. If this type of administration is not feasible, intermittent intravenous bisphosphonate preparations, such as pamidronate, may be used.<sup>56</sup> Since osteoporosis-associated morbidity has not been well studied in PWS, careful monitoring of individual therapy is necessary. A trial off bisphosphonate, with continued annual monitoring of bone density, may be attempted after an adequate bone mineral density has been achieved.

Although not specifically related to osteoporosis, it should be noted that one survey study has reported a possible 10-fold increase in the prevalence of hip dysplasia in PWS relative to the general population

(10% of 565 respondents).<sup>241</sup> This potentially important finding requires more objective confirmation, and possible etiologies have not been identified. Hip dysplasia can lead to limited mobility and degenerative hip disease.

## Respiratory and Vascular Systems

### Respiratory Disorders

#### *Physiology*

As reviewed above, respiratory disorders, including apnea, sleep-related disorders, and hypoventilation, are a major cause of morbidity in PWS, affecting at least 50% of individuals. In addition, respiratory failure is the major identified cause of mortality.

The control of normal respiration involves complex, interrelated mechanisms under both involuntary and voluntary control. The entire process of respiration involves three primary components<sup>26</sup>: (1) thoracic movement and ventilation, or exchange of air between the lungs and atmosphere; (2) exchange of gases (oxygen, CO<sub>2</sub>, etc.) across the alveolar membranes; and (3) transport in the circulation, delivery, and exchange in the tissues. The end result is maintenance of tissue oxygen and CO<sub>2</sub> homeostasis. Respiratory disorders in PWS exclusively involve the first component of respiration. No primary abnormalities of the lung tissue or oxygen/CO<sub>2</sub> transport have been identified in PWS.

The first component of respiration is dependent on coordinated neural control of the respiratory musculature, including the upper airway, thoracic muscles, diaphragm, and abdominal muscles. During inspiration, the diaphragm moves down into the abdomen, creating negative pressure in the lungs and influx of air. Additional chest wall muscles may be recruited, especially during exertion. Air entry through nasal and oral paths require coordinated actions of upper airway musculature, including pharyngeal elevation, laryngeal opening, and protective closure (e.g., during swallowing and vocalization). Expiration is primarily a passive event due to elastic recoil of the chest wall and lungs; however, chest wall and abdominal muscles may be recruited during exertion. Due to the high content of Type 1 (slow twitch) and Type 2A muscle fibers, the normal diaphragm is relatively resistant to fatigue. However, the upper airway musculature has a high proportion of fast-twitch fibers and, therefore, a greater susceptibility to fatigue.

The control of breathing is via chemoreceptors that send signals to the central nervous system. Peripheral chemoreceptors in the carotid bodies sense the partial pressure of oxygen (not oxygen content per se), as well as increased PCO<sub>2</sub>, acidemia, and low perfusion; these chemoreceptors are not essential for maintenance of respiration. Central chemoreceptors are distributed along the brainstem in several groups; these chemoreceptors respond primarily to increased PCO<sub>2</sub> and decreased pH in the cerebrospinal fluid, both changes resulting in increased respiration.

The automatic rhythmic nature of breathing is controlled by three respiratory centers, located in the brainstem pons, solitary nucleus

(dorsal medulla), and ventral medulla. The pontine respiratory group has connections to the hypothalamus and cerebral cortex, has inspiratory and expiratory functions, and may be involved in establishing respiratory patterns. The medullary centers, and particularly the pre-Bötzinger region of the ventral respiratory group, appear to be essential for establishing respiratory rhythmicity.

### *Pathophysiology*

Using a modification of the classification included in a recent review,<sup>156</sup> reported sleep and breathing disorders and representative studies in PWS are as follows:

1. Abnormalities of Daytime Breathing
  - a. Restrictive lung disease<sup>85</sup>
  - b. Abnormal ventilatory response to hypercapnia and/or hypoxia<sup>13</sup>
2. Abnormalities of Sleep and Wakefulness
  - a. Excessive daytime sleepiness<sup>43,47,48,78,97,100,101,115,125,138,224</sup>
  - b. Disorders of REM sleep
    - i. Respiratory abnormalities during rapid-eye movement (REM) sleep<sup>100,138,221</sup>
    - ii. Disordered timing of REM sleep<sup>115,138,221,226</sup>
  - c. Abnormalities of arousal—reduced arousal during sleep in response to hypoxic or hypercapnic stimuli<sup>12,132</sup>
  - d. Sleep-disordered breathing
    - i. Obstructive sleep apnea<sup>90,183</sup>
    - ii. Alveolar hypoventilation<sup>156</sup>
    - iii. Decreased oxygen saturation<sup>100,115,221</sup>
    - iv. Reduced ventilatory response to hypoxia and/or hypercapnia<sup>132,183</sup>

The etiology and PWS-specific occurrence of these respiratory disorders is controversial. For instance, some studies show a surprisingly low occurrence of sleep apnea in PWS.<sup>97,100,115</sup> The excessive daytime sleepiness bears some resemblance to narcolepsy, a multifactorial genetic condition characterized by excessive, disabling daytime sleepiness, cataplexy and sleep paralysis, and severe disturbances in REM sleep. However, the bulk of information suggests that PWS and narcolepsy are distinct.<sup>156</sup> In addition, non-PWS narcolepsy has not been associated with genes within the PWS locus.

A hypothalamic disturbance has been proposed as a common link for the observed disorders. However, as reviewed above, the major control of resting automatic respiration is at the brainstem level. Ablation of higher centers, including the hypothalamus and cortex, has minimal effect on resting respiration.<sup>107</sup> On the other hand, the hypothalamus is involved in adjusting respiration in response to hypoxia,

hypercapnia, and other sensory input, modulating cortical and brainstem outputs to affect ventilation. The extent of this influence in humans is not completely defined. In lower species, the hypothalamic response to hypercapnia is mediated by GABA, which may be of interest since several non-imprinted GABA-receptor subunit genes are located in the PWS region of chromosome 15q. In rodents, disruption of *Ndn*, an imprinted gene within the PWS region, results in deficiency of oxytocin and gonadotropin-releasing hormone neurons in the hypothalamus,<sup>149</sup> which is of interest in relation to the observed deficiency of hypothalamic oxytocin neurons in human PWS<sup>202</sup> (although CSF oxytocin levels are reported to be high in PWS<sup>139</sup>) and the variable hypogonadotropic hypogonadism, as reviewed in a previous section. Disruption of *Ndn* in rodents also leads to a disorder of respiratory drive similar to that observed in PWS; this effect may be due to a defect at the brainstem level.<sup>175</sup> However, as of this writing, no specific hypothalamic abnormalities have been identified in human PWS or animal models to account for the clinically observed respiratory disorders.

Obesity has been proposed as a possible mechanism for obstructive sleep apnea in PWS. However, as recently reviewed,<sup>156</sup> the data are controversial with some studies indicating no relationship. Obesity or, more specifically, overweight has also been postulated to contribute to restrictive lung disease in PWS, as has been described in morbidly overweight individuals without PWS.<sup>137</sup> However, data suggest that respiratory muscle hypotonia may be a more important contributory factor,<sup>85,156</sup> especially since respiratory problems can be observed without excess body weight, as in neonates with PWS.

Sleep and respiratory disorders similar to those in PWS have been described in individuals with non-PWS neuromuscular disorders.<sup>18,55,121,166,192</sup> In myotonic dystrophy, a condition often compared to PWS, a decreased number of neurons in the medullary arcuate nucleus (a postulated brainstem respiratory control center) was observed in 3 individuals with hypoventilation, as compared with 5 with myotonic dystrophy without hypoventilation and 18 controls.<sup>161</sup> Although these data were interpreted to be consistent with a primary central respiratory defect in myotonic dystrophy, it may also be consistent with retrograde loss of neurons due to peripheral muscle degeneration, weakness, and disuse, a situation that may also theoretically occur in PWS. Central, obstructive, and combined apnea, similar to the apnea described in PWS, have been characterized in non-PWS individuals with neuromuscular disease causing weakness of the respiratory musculature.<sup>121</sup>

Individuals with neuromuscular disorders may also be more prone to respiratory compromise due to normal reductions in accessory respiratory and upper airway muscle tone that occur during REM sleep,<sup>143</sup> a sleep period that appears to be particularly affected in PWS. Additional upper airway problems in PWS (e.g., decreased airway diameter, thick oral secretions, and possible adenotonsillar hypertrophy<sup>156,183</sup>) may further compound this problem.

Finally, individuals with PWS are notably deficient in growth hormone and insulin-like growth factor-I (IGF-I, also known as somatomedin-C), a growth hormone-dependent peptide (see Chapter 7). Both growth hormone and IGF-I have been directly or indirectly shown to be respiratory stimulants.<sup>181</sup> Withdrawal of growth hormone therapy in adults with non-PWS GH deficiency has been associated with a shift from obstructive to central apnea and an increase in slow-wave sleep time.<sup>157</sup>

The consequences of respiratory disorders in PWS have not been well defined, although this category of disorder is the most commonly identified cause of demise. As with other disorders involving respiratory muscle weakness, a decreased ability to compensate during acute lung disease or hypermetabolic states may account for the relatively high occurrence of pneumonia- and fever-related mortality. The decreased respiratory capacity can also lead to hypertrophy and eventual failure of the right heart (cor pulmonale), another commonly specified cause of death in PWS (see next section).

Excessive daytime sleepiness has been correlated with severity of behavior disorders in PWS.<sup>121</sup> In non-PWS individuals, obstructive sleep apnea has been correlated with risks for cardiovascular and cerebrovascular diseases<sup>165,168</sup> and a variety of other comorbidities, including diabetes mellitus<sup>248</sup> and decreased cognition and school performance.<sup>76,164,216</sup>

### *Evaluation*

The evaluation of respiratory and sleep disorders has gained recent prominence due to reports of respiratory-related mortality in children with PWS who received GH treatment<sup>158,228</sup> (see Chapter 7). An initial review by the manufacturer of Genotropin®, the GH brand labeled for treatment of PWS, revealed seven cases, all of whom had evidence of respiratory compromise (five with pneumonia) either preceding or at the time of demise ("Prader-Willi Syndrome and Death," Pfizer Global Pharmaceuticals, October 2, 2003). This led to the placement of an additional label in the package insert on April 30, 2003, including the following advisory:

Growth hormone is contraindicated in patients with Prader-Willi syndrome who . . . have severe respiratory impairment. . . . Patients with Prader-Willi syndrome should be evaluated for upper airway obstruction before initiation of treatment with growth hormone. If during treatment with growth hormone patients show signs of upper airway obstruction (including onset of or increased snoring), treatment should be interrupted. All patients with Prader-Willi syndrome should be evaluated for sleep apnea and monitored if sleep apnea is suspected.

Subsequent and previous case reviews of individuals with PWS who were *not* treated with growth hormone demonstrated that respiratory disorders are the major cause of morbidity and mortality. Consideration by the Clinical Advisory Board of PWSA (USA) recognized the overall risk for respiratory disorders in PWS, resulting in a statement that partially contradicts the Genotropin labeling (Figure 5.1).



Of these two statements, the PWSA (USA) guidelines are more consistent with clinical experience and published data. However, although these recommendations provide valuable guidance, there are limitations that prevent a completely evidence-based approach to respiratory disorders in PWS.

Most of the attention regarding respiratory disorders has focused on identification of obstructive sleep apnea (OSA). This is based largely on data in non-PWS populations showing an association of OSA with morbidity (see above); it should be noted, however, that these data are not considered to be definitive.<sup>25</sup> A recent review<sup>156</sup> found that the reported prevalence of obstructive sleep apnea in PWS ranged from 0 to 100%. Available data are limited by small sample size, biased sampling, and differences in screening and diagnostic criteria. Nonetheless, the overall impression is that a significant proportion of individuals with PWS will be diagnosed with OSA if tested, i.e., that PWS is itself a risk factor for OSA. However, it is currently unclear whether all individuals with PWS benefit from knowledge of this diagnosis in the absence of associated morbidity.

Clinical screening for OSA has been proposed in both PWS and non-PWS patients to improve the diagnostic yield of testing and/or to provide a basis for treatment. Snoring has been proposed as an indicator of clinically significant OSA in non-PWS populations. However, the diagnostic sensitivity and specificity of snoring for morbidity-associated OSA (i.e., OSA associated with cardiac, neuropsychologic, or other sequelae) have not been conclusively demonstrated in either PWS or non-PWS populations.<sup>136,210</sup> In non-PWS children, it has been stated that OSA “is very unlikely in the absence of snoring.” Snoring is dependent on both relaxation of the pharyngeal muscles and airflow; therefore, hypotonia-related hypoventilation in PWS could decrease the occurrence of snoring even in the presence of OSA. Other proposed clinical indicators of significant morbidity-associated OSA, including obesity (or overweight), sleep history, and daytime somnolence, have not been validated in PWS and are controversial in non-PWS populations.

The “gold standard” for diagnosis of OSA is nocturnal polysomnography, commonly referred to as a “sleep study,” in which various parameters (oxygen saturation, carbon dioxide content, brain wave activity, sleep/wake status) are monitored during sleep. However, the utility of this procedure is limited by cost (currently ~US\$1,000–\$1,500) and availability (particularly for pediatric testing). In addition, there is controversy over the interpretation of polysomnographic data that is only partly resolved by consensus criteria, and outcome-based normative data are not available. Abbreviated polysomnography, alternate procedures, and home monitors have even more serious limitations and cannot be recommended in PWS.

Polysomnography prior to surgery, particularly tonsillectomy/adenoidectomy, has been recommended for PWS (see above) and for children without PWS who have adenotonsillar hypertrophy and evidence of OSA. However, it is not clear how these data impact the performance of the surgical procedures. Artificial respiratory support is required

## PWSA (USA) Clinical Advisory Board, 2003 Consensus Statement

Problems with sleep and sleep-disordered breathing have been long known to affect individuals with Prader-Willi Syndrome (PWS). The problems have been frequently diagnosed as sleep apnea (obstructive-OSA, central, or mixed) or hypoventilation with hypoxia. Disturbances in sleep architecture (delayed sleep onset, frequent arousals, and increased time of wakefulness after sleep onset) are also frequently common. Although prior studies have shown that many patients with PWS have relatively mild abnormalities in ventilation during sleep, it has been known for some time that certain individuals may experience severe obstructive events that may be unpredictable.

Factors that seem to increase the risk of sleep-disordered breathing include young age, severe hypotonia, narrow airway, morbid obesity, and prior respiratory problems requiring intervention, such as respiratory failure, reactive airway disease, and hypoventilation with hypoxia. Due to a few recent fatalities reported in individuals with PWS who were on growth hormone therapy (GH) some physicians have also added this as an additional risk factor. One possibility (that is currently unproven) is that GH could increase the growth of lymphoid tissue in the airway thus worsening already existing hypoventilation or OSA. Nonetheless, it must be emphasized that there are currently no definitive data demonstrating GH causes or worsens sleep-disordered breathing. However, to address this new concern, as well as the historically well documented increased risk of sleep-related breathing abnormalities in PWS, the Clinical Advisory Board of the PWSA (USA) makes the following recommendations:

1. A sleep study or a polysomnogram that includes measurement of oxygen saturation and carbon dioxide for evaluation of hypoventilation, upper airway obstruction, obstructive sleep apnea and central apnea should be contemplated for all individuals with Prader-Willi syndrome. These studies should include sleep staging and be evaluated by experts with sufficient expertise for the age of the patient being studied.
2. Risk factors that should be considered to expedite the scheduling of a sleep study should include:
  - a. Severe obesity—weight over 200% of ideal body weight (IBW).
  - b. History of chronic respiratory infections or reactive airway disease (asthma).
  - c. History of snoring, sleep apnea, or frequent awakenings from sleep.
  - d. History of excessive daytime sleepiness, especially if this is getting worse.
  - e. Before major surgery, including tonsillectomy and adenoidectomy.
  - f. Prior to sedation for procedures, imaging scans, and dental work.
  - g. Prior to starting growth hormone or if currently receiving growth hormone therapy.

Additional sleep studies should be considered if patients have the onset of one of these risk factors, especially a sudden increase in weight or change in exercise tolerance. If a patient is being treated with growth hormone, it is not necessary to stop the growth hormone before obtaining a sleep study unless there has been a new onset of significant respiratory problems.

Any abnormalities in sleep studies should be discussed with the ordering physician and a pulmonary specialist knowledgeable about treating sleep disturbances to ensure that a detailed plan for treatment and management is made. Referral to a pediatric or adult pulmonologist with experience in treating sleep apnea is strongly encouraged for management of the respiratory care.

**Figure 5.1.** Recommendations for Evaluation of Breathing Abnormalities Associated with Sleep in Prader-Willi Syndrome.

In addition to a calorically-restricted diet to ensure weight loss or maintenance of an appropriate weight, a management plan may include modalities such as supplemental oxygen, continuous positive airway pressure (CPAP), or BiPAP. Oxygen should be used with care as some individuals may have hypoxemia as their only ventilatory drive and oxygen therapy may actually worsen their breathing at night. Behavior training is sometimes needed to gain acceptance of CPAP or BiPAP. Medications to treat behavior may be required to ensure adherence to the treatment plan.

If sleep studies are abnormal in the morbidly obese child or adult ( $IBW > 200\%$ ) the primary problem of weight should be addressed with an intensive intervention—specifically, an increase in exercise and dietary restriction. Both are far preferable to surgical interventions of all kinds. Techniques for achieving this are available from clinics and centers that provide care for PWS and from the national parent support organization (PWSA-USA). Behavioral problems interfering with diet and exercise may need to be addressed simultaneously by persons experienced with PWS.

If airway-related surgery is considered, the treating surgeon and anesthesiologist should be knowledgeable about the unique pre- and postoperative problems found in individuals affected by Prader-Willi syndrome (see “Medical News” article regarding “Anesthesia and PWS” written by Drs. Loker and Rosenfeld in *The Gathered View*, Vol. 26, Nov.–Dec. 2001). Tracheostomy surgery and management presents unique problems for people with PWS and should be avoided in all but the most extreme cases. Tracheostomy is typically not warranted in the compromised, morbidly obese individual because the fundamental defect is virtually always hypoventilation, not obstruction. Self-endangerment and injury to the site are common in individuals with PWS who have tracheostomies placed.

At this time there is no direct evidence of a causative link between growth hormone and the respiratory problems seen in PWS. Growth hormone has been shown to have many beneficial effects in most individuals with PWS including improvement in the respiratory system. Decisions in the management of abnormal sleep studies should include a risk/benefit ratio of growth hormone therapy. It may be reassuring for the family and the treating physician to obtain a sleep study prior to the initiation of growth hormone therapy and after 6-8 weeks of therapy to assess the difference that growth hormone therapy may make. A follow-up study after one year of treatment with growth hormone may also be indicated.

Members of the Clinical Advisory Board are available for consultation with physicians and families through the Prader-Willi Syndrome Association (USA).

Figure 5.1. *Continued.*

during such procedures regardless of test results and the supposition that test results may be predictive of recovery or surgical outcome has not been proven.<sup>164</sup>

In contrast to OSA and sleep studies, there has been little attention paid to routine pulmonary function testing in PWS (e.g., measurement of lung volumes, inspiratory and expiratory pressures, oxygen and carbon dioxide while awake).<sup>156</sup> Pulmonary function testing provides important measures of ventilatory capacity and respiratory muscle function, both of which are known to be abnormal in PWS. The relative lack of attention to such testing may, in part, be due to the usual need for active cooperation from the patient and consequent perceived difficulties with PWS. Nonetheless, modified pulmonary function testing data in children with PWS have been reported<sup>85,131</sup> with no significant reports of problems with test feasibility.

In summary, published data do not allow for evidence-based specific recommendations for evaluation of respiratory disorders in PWS. Experience-based recommendations, such as those proposed by PWSA (USA) (see Figure 5.1) and by Nixon and Brouillette,<sup>156</sup> provide reasonable guidance. However, consultation with clinicians with experience in the medical management of PWS is recommended before and after testing.

At the current time, it does not seem advisable to *routinely* test all individuals with PWS for OSA or pulmonary function abnormalities outside of a research protocol. A large proportion will be diagnosed with a respiratory abnormality regardless of symptomatology, and there are no data correlating the results of such testing with risks for morbidity or mortality. In the absence of this information, routine testing could cause undue cost and concern. Polysomnography and/or pulmonary function testing in PWS would appear to be most useful in two circumstances:

1. To assist with therapeutic planning for patients with definite, persistent evidence of clinically significant respiratory compromise or sleep disorder, e.g., 2a–2d of the PWSA (USA) risk factors—hypertension, evidence of pulmonary hypertension, or cor pulmonale.
2. To monitor therapies that may affect respiratory function, e.g., continuous positive airway pressure (CPAP), growth hormone.

Once a decision has been made to proceed with testing, it may be reasonable to routinely obtain pulmonary function testing and to limit the performance of polysomnography to those individuals with clinical evidence of sleep-disordered breathing or excessive daytime sleepiness, as has been recommended by Nixon and Brouillette.<sup>156</sup>

### *Treatment*

Given the high probability of finding a respiratory abnormality in an individual with PWS and the potentially invasive nature of some treat-

ment modalities, the decision to initiate treatment should be carefully considered, preferably in consultation with specialists in PWS and cardiorespiratory care. Among the points to be considered are the following:

1. The indications for the evaluation—e.g., the signs and symptoms that prompted testing. If the testing was routine and the patient is asymptomatic, is treatment indicated? Or is continued monitoring preferable?
2. The feasibility and efficacy of treatment options. In most cases, this will be based on the consultant's own knowledge and experience, limited published data in PWS, and a larger published experience in non-PWS populations (which may or may not be directly relevant).
3. Overall clinical status and expected benefits for the individual patient.

Evaluation and treatment of contributory co-morbidities should be first and foremost, even in individuals with PWS who do not have documented respiratory abnormalities. Exercise and physical therapy may help improve respiratory and general muscle tone, thereby improving ventilatory effort. Exercise and weight control may also reduce the restrictive component of respiratory impairment.<sup>34,61,101,225</sup> Bracing and, if indicated, surgical correction of significant scoliosis (see section on scoliosis) may improve pulmonary function, particularly if the curvature is severe.

In non-PWS individuals with obstructive sleep apnea, particularly those with evidence of tonsillar hypertrophy, adenotonsillectomy has been reported to improve respiratory status, snoring, and neurocognitive and other disease measures, especially over the short term. However, there is limited published experience with adenotonsillectomy and a related procedure, uvulo-palato-pharyngoplasty, in PWS,<sup>16,102,156</sup> and concerns have been raised regarding pre- and postoperative risks even in non-PWS populations.<sup>164</sup>

Nasal mask or cannula delivery of oxygen and/or ventilatory support via continuous positive airway pressure or intermittent positive pressure ventilation, usually as a nocturnal therapy, may be beneficial in patients with chronic hypoxemia, although patient cooperation can be problematic.<sup>48,156,194</sup> In the current view of these authors and according to the recommendations of the PWSA (USA) Clinical Advisory Board, tracheostomy is not a preferable treatment option in PWS.

Central respiratory stimulants, such as medroxyprogesterone, caffeine, and theophylline, have not been adequately studied in PWS and may potentially have adverse effects on behavior. Modafinil, a relatively new medication for treatment of narcolepsy and obstructive sleep apnea, has also not been studied in PWS.<sup>4</sup>

Finally, growth hormone treatment has been associated with significant improvements in pulmonary function, including resting ventilation, airway occlusion pressure, and ventilatory response to carbon

dioxide in nine children with PWS treated for 12 months.<sup>131</sup> Less significant improvements were noted with 6 months of therapy.<sup>89</sup>

### Cardiovascular and Cerebrovascular Systems

Congenital cardiac, vascular, or cerebrovascular malformations and disorders have not been reported to occur with increased frequency in PWS. In addition, hypertension appears to have a surprisingly low occurrence in PWS in view of the obesity/overweight; this could be related to the unexpectedly low occurrence of hyperinsulinemia<sup>147</sup> (see Chapter 6).

#### *Cor Pulmonale*

Cor pulmonale (from Latin: *heart of the lungs*) can be generally defined as right heart dysfunction resulting from pulmonary disease. This condition is the most commonly reported cardiovascular complication in PWS and is often cited as a cause of mortality,<sup>125,200,211,222</sup> although careful examination of the literature reveals few well-documented cases.

Clinical criteria for cor pulmonale have been controversial. Weitzenblum<sup>239</sup> proposed that cor pulmonale be defined as “pulmonary arterial hypertension resulting from diseases affecting the structure and/or the function of the lungs; pulmonary arterial hypertension results in right ventricular enlargement (hypertrophy or dilatation) and may lead with time to right heart failure.” A consensus panel sponsored by the World Health Organization<sup>142,239</sup> lists five categories of pulmonary hypertension. Categories 1 (pulmonary arterial hypertension), 2 (pulmonary venous hypertension), 4 (caused by chronic thrombotic and/or embolic disease), and 5 (caused by disorders directly affecting the pulmonary vasculature) do not appear to be relevant to PWS.

Category 3 is defined as “pulmonary hypertension associated with disorders of the respiratory system and/or hypoxemia.” Eight subcategories are included: 3.1 chronic obstructive pulmonary disease, 3.2 interstitial lung disease, 3.3 sleep-disordered breathing, 3.4 alveolar hypoventilation disorders, 3.5 chronic exposure to high altitude, 3.6 neonatal lung disease, 3.7 alveolar capillary dysplasia, and 3.8 other. As described in the preceding section, categories 3.1, 3.3, and 3.4 are most relevant to PWS.

Significant pulmonary hypertension is caused by *chronic* alveolar hypoxemia ( $\text{PaO}_2 < 55\text{--}60\text{ mmHg}$ ), as may occur with neuromuscular disease and resultant hypoventilation, or with severe obstructive apnea. Alveolar hypoxemia causes pulmonary vasoconstriction, a normal physiologic response. When this occurs chronically over a long period of time, it can lead to structural remodeling of the pulmonary vasculature and chronic pulmonary hypertension. The increased pressure causes resistance to the outflow of the right heart ventricle, leading to right heart hypertrophy or dilatation, with a risk for eventual cardiac failure. In non-PWS populations, chronic obstructive sleep apnea can be associated with a 17% to 41% occurrence of pulmonary hypertension. It has been stated that in this group of patients without intrinsic lung disease, pulmonary hypertension is rarely observed in the absence of daytime (awake) hypoxemia.<sup>142</sup>



In non-PWS patients, clinical signs and non-invasive testing for pulmonary hypertension are considered to have variable specificity (i.e., indicative of the disorder if present) and relatively low sensitivity (does not rule out pulmonary hypertension if not present) and are usually seen late in the course of disease.<sup>239</sup> These findings include peripheral edema (especially ankle edema), a typical tricuspid regurgitation murmur, accentuation of the second heart sound, electrocardiogram evidence for right ventricular hypertrophy, and increased diameter of the pulmonary artery on chest X-ray. Echocardiographic methods are considered to be the best noninvasive tests for pulmonary hypertension and right heart status, correlating relatively well with more invasive methods. Magnetic resonance imaging (MRI) and other methods may provide additional information.

The treatment of pulmonary hypertension and, particularly, cor pulmonale involves (1) provision of oxygen to prevent pulmonary hypoxemia and vasoconstriction and (2) vasodilators. Surgical intervention may be necessary in severe cases. Evaluation and treatment of these disorders are best handled by an experienced cardiologist.

As of this writing, the percentage of PWS individuals who meet stringent criteria for diagnosis of pulmonary hypertension, with or without right heart dysfunction, is not known. In addition, risk factors, clinical signs and symptoms, natural history, treatment indications, and outcomes are not defined. Peripheral edema is a not uncommon finding, particularly in adults, but personal experience suggests a low correlation with a confirmed diagnosis of right heart failure. Since hypoxemia is the major cause of pulmonary hypertension and consequent right heart failure, documentation of decreased pulmonary function, chronic alveolar hypoventilation and low PaO<sub>2</sub> (e.g., by oximetry), particularly with daytime occurrence, may be indications for further cardiac evaluation and/or referral to a cardiologist. Cor pulmonale appears to be a frequently reported cause of mortality in adults with PWS; a recommendation could be made for routine cardiac evaluation of all adults with PWS.

### *Other Vascular Conditions*

Only a few well-documented cases of coronary artery disease have been reported in PWS. A 26-year-old male with PWS and Type 2 diabetes mellitus was found to have a myocardial infarction and inoperable 3-vessel coronary artery disease after presenting with bilateral lower limb swelling.<sup>123</sup> A 28-year-old woman with PWS was found to have stenosis of the left anterior descending artery with probable myocardial infarction after presenting with chest pain.<sup>163</sup> In addition, there are scattered postmortem reports of atherosclerotic heart disease in PWS, usually as an incidental finding; this is also a common incidental finding in the general population. Biochemical risk markers for atherosclerotic heart disease (e.g., C-reactive protein, homocysteine) have not been reported in PWS.

As with ischemic heart disease, there are only scattered reports of cerebrovascular accident (stroke) in PWS. A case of apparent vaso-occlusive stroke with consequent moyamoya syndrome (revasculariza-

tion of the middle cerebral arteries) was reported in a teenager with PWS and Type 2 diabetes mellitus.<sup>120</sup>

Since ischemic vascular disease is commonly linked to obesity and sleep-disordered breathing in the general population,<sup>165,168,248</sup> the low prevalence of these conditions in PWS is surprising and may be due to the lower-than-expected occurrence of dyslipidemia and insulin-resistance (see section on Obesity). In this respect, it is notable that 2 of the 3 documented cases occurred in individuals with PWS and concurrent Type 2 diabetes mellitus.

## Miscellaneous Medical Concerns

### Thermoregulatory Disorders, Autonomic Dysfunction, and Anesthesia Risk

The ability to maintain core body temperature within a narrow range is a major characteristic of normal mammalian physiology.<sup>37,247</sup> Ambient (environmental) temperature sensation occurs via peripheral nerves that signal to a hypothalamic regulatory center, resulting in appropriate signaling back to the periphery through the autonomic and sympathetic nervous systems. A similar mechanism may be triggered with exposure to endogenous pyrogens (i.e., with febrile illness), although body temperature may be less efficiently regulated in these conditions.

During the usual resting state, body temperature (36.5°C) is higher than in the environment (~25°C); the temperature difference is largely accounted for by heat generation resulting from routine metabolic processes. During ambient temperature fluctuations, both voluntary behavioral reactions (e.g., clothing and activity) and physiologic mechanisms are important elements of thermoregulation. When ambient temperature rises, the body dissipates heat via (1) vasodilation, which increases environmental heat exchange via radiation and convection (~75% of heat loss), and (2) sweating with evaporative cooling (~25%). When ambient temperature falls, the thermogenic response includes (1) norepinephrine-stimulated vasoconstriction, leading to decreased transfer of core body heat to the skin, and (2) shivering thermogenesis, in which there is progressive recruitment of muscle fibers that undergo involuntary, rhythmic contractions resulting in heat generation. Muscle thermogenesis can be further augmented by voluntary physical exertion; however, prolonged cold exposure and exertion can lead to fatigue and declines in both exertional and shivering thermogenesis. In small mammals and human infants, nonshivering thermogenesis from brown fat is a crucial mechanism for thermoregulation; however, this mechanism appears to be minimally active in human adults.<sup>37</sup>

Clinically, thermoregulatory disorders can be defined as (1) an inability to normally regulate core body temperature in response to environmental temperature fluctuations, (2) extreme high fevers during illness, and/or (3) risk for hypo- or hyperthermia during anesthesia.

A survey study of 27 PWS individuals (2 to 46 years old) reported at a scientific meeting of PWSA (USA) found that “clinically important

abnormal temperature control is not a common event in PWS.<sup>39</sup> At the same meeting, five infants with PWS and unexplained hyperthermia (temperatures above 101°F) were reported.<sup>244</sup> In a compilation of cases used for derivation of clinical diagnostic criteria for PWS, “abnormal temperature sensitivity” was reported in 4.6% or 3 of 65 PWS subjects and none of 11 non-PWS individuals (this feature was included as a “supportive finding”).<sup>105</sup> A survey study of 85 children with PWS found an increased occurrence of febrile convulsions and hypothermia (temperature less than 94°F) as compared with 85 non-PWS siblings and 118 well children<sup>243</sup>; however, there were no differences from a group of 105 non-PWS neurodevelopmentally-impaired children. Hypothermia (rectal temperature 30°C) with complete recovery has been reported in a 5-month-old infant with PWS who may have been exposed to a very low ambient temperature.<sup>238</sup> Hyperthermia during illness was also postulated to contribute to mortality in several infants with PWS, possibly due to increased respiratory demand and compromise.<sup>200</sup> Together, these reports suggest but do not confirm a possible risk for temperature dysregulation in infants with PWS.

A cold-exposure study was conducted in 6 PWS subjects and 3 non-PWS individuals placed into a cold-room with temperature set at 4°C with light clothing for 1 hour.<sup>29</sup> Rectal (core) temperatures were noted to rise in all 3 non-PWS and 2 PWS individuals. Rectal temperature showed a small decrease in 3 of 6 PWS subjects, implying a defect in cold-adaptation.

Temperature dysregulation has also been reported in a 37-year-old woman with PWS who had three separate episodes of hypothermia (27°C–32°C) associated with infections.<sup>167</sup> The risk for hypothermia was attributed to the use of risperidone, a dopamine and serotonin type 2 receptor antagonist. Hypothermia resolved after cessation of risperidone but recurred with use of olanzapine, a similar medication. Hypothermia has also been reported with these medications in non-PWS individuals<sup>24</sup> and with other psychotropic medications that are often used in PWS<sup>118,119</sup>; therefore, it is not clear whether the risk is greater for individuals with PWS.

Autonomic dysfunction has been proposed as a mechanism for the possible disorders of thermoregulation in PWS. The autonomic nervous system regulates smooth muscle, exocrine glands, and cardiac muscle and is largely responsible for maintaining somatic homeostasis through involuntary mechanisms. This is distinguished from the somatic motor system, which is responsible for primarily voluntary control of skeletal muscles. The hypothalamus is considered to be the control center for the autonomic system; however, multiple areas of the cerebral cortex, brain stem, cerebellum, and spinal cord also play roles. The autonomic system is divided into the sympathetic and parasympathetic systems. The sympathetic system arises from spinal cord neurons, giving rise to segmental innervation of smooth muscle in the eye, heart, GI tract, and reproductive organs. The parasympathetic system arises from both brainstem neurons, including cranial nerves III, VII, IX, and X (vagus nerve) and sacral neurons, and is largely responsible for peristalsis and exocrine secretion.

Evidence for a generalized autonomic (parasympathetic) dysfunction in PWS is based primarily on a study of 14 subjects with PWS (4 to 40 years old, 8 female) and a comparison group of individuals without PWS.<sup>65</sup> Within the PWS cohort, 50% had abnormal pupillary constriction to pilocarpine and, on EKG, 6 of 14 had an abnormal ratio of the 30th to 15th R-R interval. A higher resting pulse and lower orthostatic pulse response was correlated with body mass index (BMI). Decreased frequency of respiratory sinus arrhythmia was also reported.<sup>63</sup> A later study in 32 individuals with PWS in a thermoneutral environment (72°F) was interpreted to show that resting cutaneous temperature and capillary blood flow were not different from controls, thereby supporting a theory of central as opposed to peripheral autonomic dysfunction,<sup>64</sup> although the data presented seem to show higher capillary blood flow and mean cutaneous temperature in the group with uniparental disomy ( $n = 9$ ) as compared with the deletion cases ( $n = 23$ ) and controls ( $n = 5$ ). Contrary to these findings, a detailed study in 26 individuals with PWS showed no differences in autonomic regulation of cardiac function as compared with age-, gender-, and BMI-matched controls.<sup>231</sup>

Deficient sweating in response to environmental warming has been anecdotally mentioned as evidence for thermoregulatory and autonomic dysfunction in PWS. However, there are no published studies characterizing this condition. Other evidence for autonomic dysfunction, such as decreased ability to vomit and decreased salivation, are discussed in the next chapter.

Therefore, there is no current evidence that autonomic dysfunction accounts for thermoregulatory defects in PWS. In view of the normal physiologic dependence on shivering thermogenesis during exposure to cold, a risk for core hypothermia may be related to the decreased muscle mass.

Disordered thermoregulation during general anesthesia has also been raised as a concern in PWS, particularly the risk for malignant hyperthermia. This anecdotal concern arises in part from the known increased risk for malignant hyperthermia in congenital myopathies, such as congenital myotonia and muscular dystrophy. Malignant hyperthermia is caused by a disorder of calcium transport in skeletal muscle, leading to increased intracellular calcium, uncoupling of mitochondrial oxidative phosphorylation, and excess heat production to several times greater than normal.<sup>87,179</sup> Clinically, the condition may be triggered by several general anesthetic agents and muscle relaxants, and is initially characterized by muscle rigidity, hyperthermia, and acidosis. To date, there are no documented reports of malignant hyperthermia or defects of muscle calcium transport in PWS.

A similar but pathologically unrelated condition, neuroleptic malignant syndrome, has been reported as an idiosyncratic reaction to a variety of psychotropic agents,<sup>71,87</sup> including several that are often prescribed in PWS. These agents are thought to trigger an inappropriate hypothalamic response by inhibiting dopamine or enhancing serotonin action, leading to muscle rigidity and hyperthermia. In addition, use of serotonin reuptake inhibitors, particularly in combination with other

agents affecting serotonin action, has been associated with “serotonin syndrome” in non-PWS individuals.<sup>87</sup> Serotonin syndrome is characterized by hyper-reflexia, tremor, muscle rigidity, autonomic dysfunction, mental confusion, and variable occurrence of hyperthermia, resulting from the muscle contractions. There are no published reports of either neuroleptic malignant syndrome or serotonin syndrome in PWS, despite the widespread use of potential triggering agents.

Finally, there have been no reports of postoperative core hypothermia with postanesthetic shivering in PWS. In non-PWS patients, this condition is considered to be an important adverse event during postoperative recovery and is thought to be due to inhibition of thermoregulation by general anesthetic agents.<sup>67</sup>

A review of eight cases of children with PWS undergoing general anesthesia showed no particular complications that were not related to obesity,<sup>60</sup> e.g., difficult intravenous access and sleep apnea. Similar data in adults with PWS have not been presented.

In summary, clinical experience suggests that a proportion of individuals with PWS may be at risk for thermoregulatory disorders, particularly environment-related hypothermia, which could be related to a diminished capacity for shivering thermogenesis. A clinically significant risk for temperature dysregulation may be particularly noted for infants with PWS, who may be prone to both hyperthermia with illness and hypothermia with environmental cold exposure. Unfortunately, however, there are insufficient data to answer the question of whether specific thermoregulatory abnormalities are more common in PWS and no conclusive proof of autonomic dysfunction. In addition, there are no data to indicate an increased risk for malignant hyperthermia, neuroleptic malignant syndrome, or serotonin syndrome. Nevertheless, in view of the relative paucity of published data and the potentially serious nature of these conditions, practitioners should be aware of the possible risks when confronted with specific situations.

## Ophthalmologic Disorders

Esotropia has been reported in 43% of 15 infants and 66% of 65 older individuals with PWS, and was included as a supportive finding for clinical diagnosis.<sup>105</sup> However, there are surprisingly few published studies characterizing ocular abnormalities and their treatment in PWS, and documentation of ophthalmologic findings is lacking in many descriptive series of the syndrome.

Esotropia is a type of strabismus (dysconjugate eye movement) in which one eye turns inward (toward the nose) while the other is fixated in a forward gaze. In a series of 46 patients clinically diagnosed with PWS, 22 were found to have esotropia, while 7 had exotropia, or outward turning of the eye.<sup>98</sup> Additional defects included myopia (15%), significant astigmatism (oblong deformation of the eye leading to blurred vision, 41%), amblyopia (decreased visual acuity in one eye, 24%), and iris transillumination defects (33%). In a detailed study of 12 patients with PWS, Roy et al.<sup>180</sup> found only 1 patient with esotropia, 2

with exotropia, and 9 with orthophoria (normal conjugate eye movements). One patient had myopic chorioretinal degeneration, 1 had disc atrophy and foveal hypoplasia, and 5 (42%) were noted to have telecanthus (increased distance between the inner corners of the eyes without orbit displacement).

A later series by Fox et al.<sup>74</sup> compared 20 PWS patients with deletion and 7 with uniparental maternal disomy with 16 controls matched for age, body composition, and intelligence. Strabismus was found in 6 deletion subjects (30%), 4 disomy subjects (57%), and 4 controls (25%)—not significantly different between groups. Abnormal iris transillumination was found in 4 deletion and none of the disomy or control subjects. Foveal hypoplasia was not identified in any of the groups, while findings of astigmatism, amblyopia, and anisometropia were not significantly different between the PWS and control groups. Stereopsis differed ( $p < 0.002$ ) between the PWS (45% deletion, 43% disomy) and controls (81%), indicating an increased defect in 3-D perception in the PWS group. The mean level of myopia was also different ( $p = 0.01$ ) between control (refractive error  $-2.33 \pm 1.65\text{SD}$ ) and PWS ( $-5.56 \pm 5.38$ ) subjects.

Ocular hypopigmentation has also been noted in PWS.<sup>103,129,234</sup> Generalized skin hypopigmentation is a well-known feature of PWS (~50% of cases) and may be associated with deletion of the *P* (pink-eyed dilution) gene, a nonimprinted gene located within the PWS deletion boundaries.<sup>30,198</sup> Mutations of the *P* gene are the cause of oculocutaneous albinism type 2 (OCA2) in humans, in which there is hypopigmentation of the eyes, skin, and hair. Associated findings include strabismus, loss of stereopsis, nystagmus, and foveal hypoplasia, apparently due to abnormal routing of the optic nerve pathways.<sup>30</sup> The similarity of these eye findings along with skin hypopigmentation to features of PWS suggested a similar pathogenesis. An initial study of 6 patients with PWS and strabismus found abnormal visual-evoked potentials (VEP) in 3 of 4 hypopigmented patients and in neither of the 2 normally-pigmented patients.<sup>52</sup> The VEP abnormality was indistinguishable from that observed in OCA2, suggesting a similar abnormality in optic nerve pathways in PWS. However, the presence of strabismus in those patients with normal VEP was unexplained and subsequent studies failed to confirm these initial findings.<sup>11,180,234</sup>

Overall, the data suggest that strabismus, both esotropia and exotropia, is not uncommon in PWS, and may be related to ocular muscle hypotonia.<sup>98</sup> A variety of other ophthalmologic disorders may also be present, including ocular hypopigmentation. These disorders could be related to deletion of the *P* gene, which is also associated with skin hypopigmentation. However, this link is far from certain because misrouting of optic nerve pathways, such as observed in OCA2, has not been confirmed in PWS.

Evaluation and treatment of eye conditions in PWS requires consultation with an experienced ophthalmologist. Treatment of congenital strabismus has been noted to have variable outcome in non-PWS cases<sup>81,83</sup> and there are limited data in PWS.<sup>93</sup>



## Sensory Function

Decreased peripheral and deep pain sensation is a commonly reported feature of PWS and, in the authors' clinical experience, a definite characteristic of the condition. However, published data relating to pain sensation in PWS is remarkably scant. Decreased pain sensation has been reported in 18% of individuals with PWS, with other reports indicating decreased pinprick sensitivity and decreased dermal and epidermal innervation.<sup>40,103</sup> In the formulation of diagnostic criteria for PWS, a high pain threshold was reported in 9% of 65 typical PWS, 9% of 11 atypical PWS, and 9% of 11 control subjects.<sup>104</sup> Easy bruising has also been anecdotally reported in PWS<sup>40</sup> and could, in part, be related to the decreased ability to feel pain; no other contributory factors have been identified.

Interestingly, disruption of the *Ndn* gene (an imprinted gene in the human PWS locus) in mice leads to increased skin-scraping behavior,<sup>149</sup> which may be analogous to the skin-picking behavior in human PWS that has been theoretically related to aberrant sensory input.

Detailed studies in five children with PWS showed normal tactile perception (stereognosis), normal sensory nerve conduction (normal myelination), and a 50% reduction in sensory nerve action potentials.<sup>28</sup> These latter results suggest that decreased density of peripheral nerve fibers may account for the decreased pain sensation.

A possible etiology for decreased somatic pain sensation was recently proposed by Lucignani et al.,<sup>135</sup> who found a reduction in gamma-aminobutyric acid type-A (GABA-A) receptors in areas of the cerebral cortex that are related to pain response in six young adults with PWS (all deletion). The GABA-A receptor is composed of several subunits, three of which are coded by nonimprinted genes in the PWS-region of chromosome 15q.

In view of the decreased pain sensation, it is important for caretakers to be vigilant for signs of infection and injury that might otherwise be signaled by pain or discomfort. Acute or unexpected changes in behavior, mobility, or gait may warrant further investigation.

## Mitochondrial DNA

The mitochondria are intracellular organelles that are ancestrally derived from bacteria and live in the mutually supportive environment of the host cells.<sup>10</sup> Mitochondria-dependent metabolic pathways, involving electron transport and oxidative phosphorylation, are the major source of energy in human cells. Some of the proteins involved in these processes are coded in the mitochondrial DNA while others are coded in the nuclear DNA of the cell, demonstrating an evolved symbiotic relationship. A variety of human disorders, primarily involving muscle and central nervous system abnormalities, have been associated with defects in these genes.

As of this writing, none of the genes involved in the Prader-Willi region of chromosome 15q have been associated with mitochondrial function or cell energetics. However, the similarities of the muscle

hypotonia in PWS to some types of mitochondrial myopathy have raised suspicions that there may be a relationship. Thus far, three cases of mitochondrial myopathy have been identified in children with PWS. A 2-year-old child with PWS and mitochondrial myopathy (complex I/IV respiratory chain deficiency diagnosed by muscle biopsy) was reported to have had open heart surgery for atrial septal defect under general anesthesia without complications.<sup>187</sup> Two cases of PWS (maternal uniparental disomy) with mitochondrial myopathy (complex I deficiency) were reported in an abstract<sup>237</sup>; the diagnosis of mitochondrial myopathy was apparently pursued because of the neonatal hypotonia and the delayed clinical suspicion of PWS. The authors concluded that the mitochondrial myopathy was "likely a secondary rather than a primary event." However, the co-occurrence of these two relatively uncommon conditions suggests the possibility of a common pathogenesis and a need for larger-scale screening studies. A recent case of fatal metabolic acidosis in an infant with PWS is also suggestive of mitochondrial DNA disease.<sup>249</sup>

There has been recent interest in the relationship of coenzyme Q10 (CoQ10) and PWS. CoQ10 is a protein encoded by the nuclear, rather than mitochondrial, DNA that plays an essential role in mitochondrial and extra-mitochondrial electron transport, as well as a variety of other vital functions.<sup>213</sup> The CoQ10 gene is not located in the PWS region. Low blood levels of CoQ10 have been identified in several disorders, including Alzheimer's, Huntington's, and Parkinson's diseases, and in some studies there is a suggestion that CoQ10 therapy may be beneficial for some of these conditions.<sup>189</sup> Low blood levels of CoQ10 in children with PWS were reported in an abstract<sup>114</sup> and beneficial effects on neurodevelopment were reported for one infant. However, a recent report found that although plasma CoQ10 levels were lower in 16 individuals with PWS as compared with controls, the levels were not different from a group of obese individuals.<sup>32</sup> The authors postulated that the lower plasma CoQ10 levels were due to the lower muscle mass and decreased energy expenditure in PWS. In view of these latter data and a lack of studies showing treatment efficacy, CoQ10 is not currently recommended as a medical therapy for PWS.

## Epilepsy

Epilepsy is defined as a disorder of the central nervous system that causes convulsions (seizures). The physical manifestations of epilepsy range from subtle changes in behavior to major episodes of generalized involuntary motor activity. Various environmental factors, including increased body temperature, may increase the propensity or threshold for generation of the abnormal electrical impulses in the brain that lead to seizures.

There have been occasional reports of epilepsy or seizures in individuals with PWS<sup>230</sup> and a suggestion that infants with PWS may be susceptible to febrile convulsions (see above); however, several systematic population surveys have failed to mention epilepsy as a specific feature of PWS.<sup>104,133,170</sup> On the other hand, epilepsy is a well-

characterized feature of Angelman syndrome<sup>79</sup> and is also associated with other chromosome 15q11–q13 defects, including interstitial duplications of maternal origin within the imprinted region.<sup>46,205,208,233</sup> A recent study of children referred from general pediatrics and neurology clinics reported a history of febrile seizures in 18 of 40 individuals (45%) with PWS and deletion, as compared with 1 of 14 patients (7%) with maternal uniparental disomy.<sup>219</sup> The same group reported seizures in 42 of 47 patients (89%) with Angelman syndrome and deletion, as compared with 4 of 9 patients (44%) with paternal uniparental disomy.<sup>220</sup> As noted by the authors, these results suggest that a lowering of the seizure threshold, leading to a risk for febrile seizures in PWS and all seizures in Angelman syndrome, could be due to haploinsufficiency of a nonimprinted seizure-related gene, such as those that code for subunits of the gamma-butyric acid receptor. Additional studies to clarify these relationships are necessary.

## Cancer

Concerns have been raised regarding the possible association of PWS with increased risk for cancer. In 1985, Hall<sup>86</sup> published three cases of leukemia in individuals with PWS. No additional cases were presented until 1999, when Cassidy et al.<sup>42,57</sup> reported results from a survey study of the PWSA (USA) membership. Of 1,077 valid responses (from 1,852 members surveyed), there were 32 confirmed cases of cancer, of which 19 were benign; 3 of 53 deaths were attributed to cancer. Eight cases involved cancer types that are monitored by the Surveillance, Epidemiology and End Results (SEER) Program, a project of the U.S. National Cancer Institute, including 3 myeloid leukemia (1 acute, 2 chronic, probably the same cases previously published by Hall). Other SEER-listed tumors in PWS included single cases of seminoma, dermatofibrosarcoma, ovarian teratoma, Hodgkin's lymphoma, and cardiac lymphoma. The 8 observed cases were compared with the calculated expected number of 4.8 (based on data from SEER), indicating that there may be an increased overall occurrence of cancer in PWS.

Other cases of cancer reported in PWS include single cases of poorly differentiated hepatoblastoma in a 16-month-old boy (deletion 15q),<sup>92</sup> hepatocyte adenoma in an 11-year-old girl with known hepatic steatosis (fatty liver),<sup>203</sup> "pseudo-Kaposi" sarcoma in a 25-year-old male,<sup>66</sup> and multiple endocrine neoplasia type 1 (MEN 1).<sup>151</sup>

Abnormalities of chromosome 15q, which is the location of the PWS region, are frequently found in tumor tissues from patients without PWS. Such tumors include breast cancers, bladder carcinoma, lymphoblastic leukemia, and myeloid leukemia.<sup>45,96,153,246</sup> The 15q abnormalities identified in these conditions include deletions, translocations, loss of heterozygosity, and duplications. In detailed studies, it appears that there may be tumor suppressor genes located distal to the Prader-Willi region,<sup>96,153</sup> loss of which may lead to tumorigenesis. The relevance of these findings to PWS is currently unknown and tumor karyotype information is lacking for most cases of cancer in PWS.

## Infections

Individuals with PWS may be prone to a variety of infections. However, any increased risk of infection appears to be primarily related to other characteristics of the syndrome. Primary immunodeficiency disorders have not been reported in PWS.

As described in previous sections, respiratory infections are a frequent cause of morbidity and mortality in PWS. The risk for serious respiratory infection is probably due to hypotonia of the respiratory musculature and consequent poor ventilatory capacity and reserve rather than inherent susceptibility to particular pathogenic organisms. Given the known risks for respiratory decompensation, judicious use of antibiotics should be considered if there is evidence of infection, even if a specific agent cannot be identified.

Dental infections are also common, as described in the next chapter, and are likely related to defects in salivation, high intake of sugar, and poor hygiene.

Skin infections are frequently observed in PWS. Contributory factors include obsessive skin picking (discussed elsewhere in this text) and decreased pain sensation, allowing traumatic skin injuries to progress to infection. All individuals with PWS should be examined regularly for cutaneous infections, particularly at pressure points (feet, buttocks) and in less-visible areas (scalp, perianal area, groin, axillae). In most cases, infected lesions can be successfully managed with topical antiseptics and topical or oral antibiotics. Culture and sensitivity studies should be considered for persistent or unusual infections, and attention should be given to infectious agents endemic to the community, such as methicillin-resistant staph aureus. Finally, the presence of systemic symptoms or acute onset of unusual behavior, body temperature instability, respiratory compromise, or uncharacteristic body movements may signal the presence of a deep tissue or systemic infection, such as osteomyelitis or pneumonia.

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# Gastrointestinal System, Obesity, and Body Composition

Ann O. Scheimann, Phillip D.K. Lee, and Kenneth J. Ellis

Obesity or overweight is arguably the most obvious physical feature of PWS. Perhaps for this reason, more than 80% of the over 1,600 publications to date regarding PWS mention, discuss, and/or explore the topic of obesity. Despite this attention, the diagnosis, pathogenesis, optimal treatment, monitoring, and outcome of this condition in PWS remain undefined. In addition, the paradox of the underweight infant with PWS evolving into an overweight child and adult has led to considerable speculation regarding pathophysiology.

In addition to the obvious physical feature of obesity/overweight and questions regarding optimal nutritional management, a variety of gastrointestinal (GI) disorders have been identified in PWS, with frequencies similar to respiratory disorders. A description of the GI system and related disorders in PWS will start this chapter, followed by a discussion of obesity and related nutrition and medical issues. Finally, a discussion of analytical methods for body composition analysis and their application in PWS is presented (see Chapter 5 for a complete outline of Part II).

## Gastrointestinal System and Disorders

The primary function of the gastrointestinal system is to facilitate intake, digestion and absorption of nutrients. The elements of the system and their functions are as follows:

1. Oropharynx and Esophagus: sucking, mastication (chewing and softening of food), salivation, swallowing (deglutition), transfer of food to the stomach
2. Stomach and Intestines: digestion, production of regulatory hormones, absorption of nutrients and elimination of waste

Elements of these processes may be relevant to the pathophysiology of PWS. Therefore, each of the following sections begins with a very brief description of the relevant physiology, followed by a review of PWS-related pathophysiology and treatment.

## Oropharynx

### *Physiology*

In the resting state, in which a person is not eating or vocalizing, the oral cavity undergoes continual involuntary salivation and swallowing. Saliva is derived primarily from the parotid, submandibular, and sublingual glands in the oral cavity (90%); another 10% is derived from scattered salivary glands. An average adult produces 0.5 to 1.5L per day. Saliva is composed primarily of water with dissolved proteins, enzymes, and minerals; the composition differs according to the source gland. The major functions of saliva include lubrication and cleansing of the oral cavity, neutralization of acids, inhibition of microbial growth, and protection of dentition.<sup>133,157</sup>

Taste, smell, and palatability are among the initial food qualities that determine intake and retention of substances in the oral cavity. After entry of solid or semisolid food into the oral cavity, a complex neuromuscular process of chewing (mastication), salivation, and swallowing (deglutition) follows. In the neonatal period, ingestion of liquid substances normally involves primarily deglutition (without mastication), and the physical mechanisms differ somewhat from that which occurs with solid food ingestion.

Mastication combines a number of processes, including reduction of food to smaller pieces suitable for deglutition. The teeth serve as passive tools for this process and are controlled by coordinated activity of the powerful jaw muscles.<sup>102,187</sup> The muscles of the tongue participate in churning and mixing of food in the oral cavity and movement of food toward the esophagus. Coordinated movement of the jaw, laryngeal, and pharyngeal muscles occurs both voluntarily and involuntarily, with neurosensory input and feedback.<sup>119</sup> Mastication may also play a role in feedback regulation of appetite,<sup>163</sup> although this has yet to be demonstrated in humans.

Increased salivation occurs in anticipation of food intake (e.g., via visual and olfactory inputs), during taste (gustatory stimulus), and during mastication. The neural inputs for this process have been summarized.<sup>157</sup> Gustatory input via cranial nerves VII (facial), IX (glossopharyngeal), and X (vagus) and masticatory input via cranial nerve V (trigeminal) to the brainstem salivary center is then relayed back to the salivary glands via cranial nerves VII (to the submandibular and sublingual glands) and IX (to the parotid glands), resulting in increased salivation. The stimulated parotid gland, which produces an amylase-rich saliva, can reach 50% of total production during mastication. During mastication, saliva has key roles in enhancing taste perception, solubilizing food products, initiation of starch and lipid digestion, and preparation of food boluses for swallowing.

The process of swallowing starts with movement of processed food toward the back of the oral cavity, accomplished primarily by voluntary movement of the tongue. The second stage involves a reflex elevation of the pharynx and peristaltic movement of the food into the esophagus. The larynx also elevates, with closure of the epiglottis, thereby protecting the airway during swallowing.<sup>171</sup> The final stage of

swallowing involves anterograde esophageal peristalsis, resulting in movement of the food bolus into the stomach. Swallowing is mediated by input via cranial nerves IX and X to the brainstem swallowing center, with output via cranial nerves V, VII, IX, X, and XII.<sup>64,157</sup> The entire process of swallowing is facilitated by saliva, which provides the necessary lubrication. In addition, saliva buffers the oropharynx and esophagus against acidic food and back leakage of gastric acid.

The human neonate relies exclusively upon the sucking reflex for nutrient ingestion.<sup>70</sup> The suck reflex develops relatively early during fetal life and involves intra- and peri-oral stimulation, leading to activation of brainstem centers interacting with the motor cortex, leading to rhythmic motor activity mediated by cranial nerves V, VII, and XII. Nonnutritive sucking (e.g., use of a pacifier) may have somewhat different dynamics and regulation from nutritive sucking (i.e., breast- or bottle-feeding),<sup>70</sup> the latter presumably involving additional coordination with swallowing. Although a sucking motor pattern can be identified in the 10- to 12-weeks' gestation fetus, coordination of sucking, swallowing, and respiration does not occur until after 35 weeks.<sup>89,144</sup> As with oral food intake after the neonatal period, the suck reflex is highly dependent upon oropharyngeal muscle tone and function.

### *Pathology in PWS*

Generalized hypotonia in the neonate with PWS is manifested by an extremely weak suck reflex, lacking in both strength and endurance.<sup>87</sup> In addition, apparent lack of coordination between suck/swallow and breathing has been anecdotally observed in some infants. Although not yet studied in detail, hypotonia of the laryngeal, pharyngeal, and esophageal musculature could lead to further problems with swallowing, airway protection, and efficient movement and retention of liquid in the stomach.

Although the oropharyngeal hypotonia usually improves sufficiently to allow adequate oral nutrition by 6 to 12 months of age, the underlying problem probably continues throughout the life span. Older individuals with PWS are often noted to avoid meat and other foods that require a relatively high oromotor effort, which may in part account for the noted preference for carbohydrates over protein.<sup>69</sup> Micrognathia and microdontia (small lower jaw and teeth), noted in some individuals with PWS, may further compound the problem by providing less muscle bulk and surface area.

Perhaps even more problematic is the lack of adequate salivation. Unusually viscous saliva has been noted in the majority of patients with PWS,<sup>22,105</sup> and decreased volume of saliva is virtually universal. Saliva collection and analysis from 25 individuals with PWS (1 to 53 years old) showed an unstimulated salivary flow rate of 0.16 g/min, as compared with 0.54 g/min in controls.<sup>94</sup> Stimulation of salivary flow by mastication of paraffin increased the flow to only 0.38 g/min, as compared with 2.38 g/min in controls (it should also be noted that saliva could not be collected from an additional 15 PWS subjects due to inadequate flow and/or viscosity). PWS saliva was noted to be extremely viscous, with increased concentrations of all measured

solutes, including fluoride (165%), calcium (226%), phosphorous (157%), chloride (124%), sodium (154%), and protein (126%). No differences were noted between the 3 uniparental disomy and 17 deletion subjects (5 did not have detailed genetic studies). A similar, but not entirely identical, condition of decreased salivation and hyperconcentration of salivary fluid has been noted in non-PWS patients with denervation of the parotid gland.<sup>130</sup> However, a normal but prominent appearance of the three major salivary glands, despite decreased salivation, was noted in one subject with PWS.<sup>204</sup>

Decreased salivary secretion, or xerostomia ("dry mouth"), leads to decreased natural cleansing of the oral cavity, severe dental caries, enamel erosion, infection, and tooth loss.<sup>7,11,94</sup> These disorders are similar to those observed with xerostomia associated with other conditions.<sup>133</sup> Enamel erosion is due to inadequate salivary buffering of food-derived acids from citrus, acidic substances (including carbonated sodas, both regular and diet), and bacterial metabolism of dietary sugar and starch,<sup>18,204</sup> resulting in resorption of bone mineral in the acidic milieu.

In non-PWS patients, xerostomia has been associated with speech abnormalities (dysphonia), a sensation of thirst resulting in frequent sipping, oral discomfort, difficulty with mastication and swallowing, taste disturbances (dysgeusia), heartburn, and halitosis.<sup>133,157</sup> Several of these features are also noted in PWS, although direct cause/effect relationships have not been systematically studied.

### *Treatment*

In neonates with PWS, hypotonic suck and lack of a coordinated feeding mechanism can often lead to a severe failure-to-thrive. Nasogastric tube-feeding is often used to meet nutritional needs,<sup>79</sup> and many infants require gastrostomy tube placement to facilitate feeding for the first few months of life.

The use of treatment strategies to improve oromotor strength and coordination of swallowing can significantly enhance feeding success. Such strategies may include early introduction of occupational and speech therapies, use of adaptive devices, positioning strategies, jaw-strengthening exercises, thickening agents for liquids, and use of low-calorie binding agents. These therapies reduce the need for parenteral (tube) feedings, as shown by our experience at Texas Children's Hospital (Figure 6.1). Infants with PWS who received supplemental oromotor therapy required nasogastric feedings for a mean of 40 days, as compared with 234 days for infants who did not receive this therapy ( $p = 0.003$ ).

Occupational and speech therapy are often utilized after the neonatal period (see separate chapters); the efficacy of these treatments in relation to feeding behavior and food preferences has not been studied in PWS, and there is poor documentation of results in other forms of dysphagia associated with muscle disease.<sup>101</sup> Nonetheless, these therapies are generally recommended for individuals with PWS.

Nonpharmacologic treatment of xerostomia in non-PWS patients often involves the use of natural secretagogues (e.g., sour lozenges,

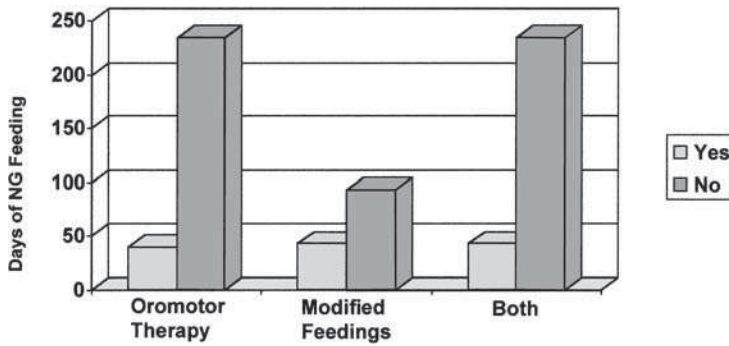


**Figure 6.1.** Impact of supplemental therapies on the duration of nasogastric tube feedings in infants with PWS (total N = 15). The y-axis is the mean number of days that nasogastric feedings were required. The x-axis shows supplemental therapies that were administered. (Source: A. Scheimann, unpublished data.)

sugarless chewing gum) to provide continuous salivary gland stimulation. This approach has been reported in some individuals with PWS,<sup>204</sup> but larger scale studies have not been conducted. Pharmacologic treatment of xerostomia has relied primarily upon topical application of artificial saliva, although the use of salivary secretagogues is increasing<sup>161</sup>; these modalities have not been studied in PWS.

Given the high risks for severe dental caries and infection, regular dental care must be established for all individuals with PWS. Oral hygiene should be instituted in infancy, even if dental eruption has not yet occurred, using soft foam toothbrushes and wetting solutions. This may be particularly important for infants on parenteral feedings, where there is virtually no stimulation of salivation or wetting from oral feeds. Fluoride treatment may also be recommended. For treatment of caries, adhesive dental techniques have been recommended.<sup>18</sup>

Avoidance of sugars, thick starchy foods, citrus, carbonated drinks, and other acidic foods is advisable. In addition, individuals with PWS should be encouraged to include copious amounts of water with each meal to facilitate mastication, swallowing, and oral cleansing.

## Stomach and Intestines

### *Physiology*<sup>50</sup>

After swallowing, esophageal peristalsis results in delivery of food boluses into the antrum of the stomach. In the resting condition, the lower esophageal sphincter, composed of specialized smooth muscle cells (not a true sphincter) maintains a positive pressure to prevent gastric contents from moving back into the esophagus. During swallowing, this pressure is released in response to local stimuli, including vasoactive intestinal peptide (VIP) and nitric oxide, thereby allowing food to enter the antrum of the stomach.

The stomach, which begins at the lower esophageal sphincter and ends at the pyloric sphincter, is composed of inner circular and outer longitudinal layers of smooth muscle which undergo rhythmic

contractions controlled by a pacemaker located in the main portion of the stomach. The stomach is lined by secretory cells, including parietal, chief, and mucus cells. In response to food-related stimuli (smell, visual, cerebral), the vagus nerve signals release of acid from the parietal cells; this effect is mediated by histamine and gastrin. The acid environment, in turn, inhibits further gastrin release and also stimulates local production of somatostatin, which inhibits histamine and gastrin release. The parietal cells also produce intrinsic factor, which is required for absorption of vitamin B<sub>12</sub>.

Vagal stimulation also results in release of pepsinogen from the chief cells of the stomach. In the presence of gastric acid, pepsinogen is processed to pepsin, which is the major enzyme involved in the initial steps of protein digestion.

Neurons within the stomach produce a number of substances that participate in regulation of gastrin, histamine, acid, and somatostatin release. These include acetylcholine and calcitonin gene-related peptide from the vagus nerve and pituitary adenylate cyclase-activating peptide, VIP, gastrin-releasing peptide, galanin, and nitric oxide from enteric neurons. Some of these peptides are also postulated to affect normal eating behavior and are discussed in the section on obesity.

When liquid substances enter the stomach, vagal stimulation results in relaxation of the proximal stomach, where the liquid is retained until gastric emptying. Solid foods are mixed, digested, and reduced to small particles in the distal stomach. Gastric emptying is accomplished by both muscular contractions of the stomach and by alternate opening and closure of the pyloric sphincter, which is under sympathetic and vagal control, respectively.

After passing through the pyloric sphincter, partially digested material enters the duodenum, where the fat, protein, and gastric acid stimulate duodenal production of cholecystokinin (CCK) and secretin. These peptides are absorbed into the bloodstream and travel to the pancreas, activating vagal stimulation of pancreatic enzyme secretion into the intestinal lumen. Duodenal distention also leads to pancreatic enzyme secretion through direct vagal stimulation (enteropancreatic reflex). These enzymes include (1) pancreatic amylase, which digests carbohydrates to oligosaccharides; (2) lipase and colipase, which digest fat (triglycerides) to monoglycerides and fatty acids; and (3) trypsin, chymotrypsin, and elastase, which digest peptides (resulting from pepsin digestion of proteins in the stomach) to oligopeptides.

Further digestion into amino acids, fatty acids, monoglycerides, and monosaccharides occurs in the small intestine. These nutrients are absorbed into the bloodstream from the intestinal lumen. In addition, the small and large intestines are responsible for absorption of water and electrolytes. Finally, the large intestine and anal sphincter are responsible for the process of solid waste elimination, or defecation.

A number of peptides are released from the gastrointestinal tract and pancreas into the bloodstream during the process of food intake, digestion, and absorption. These include insulin, glucagon, and postulated appetite-regulatory hormones. Some of these peptides are discussed in the section on obesity.



***Pathology and Treatment in PWS***

*Retrograde Movement of Ingested Substances:* Normally, ingested nutrients move in an anterograde (forward) fashion from the mouth to stomach to intestines with minimal backflow. Retrograde movement of food from the stomach into the oropharynx may occur under two primary circumstances: (1) gastroesophageal reflux and (2) emesis. Voluntary regurgitation and reprocessing of food from the stomach, or rumination, may also occur. Retrograde movement of intestinal contents has been observed in cases of severe obstruction and constipation in patients without PWS, but these problems have not been reported to be a particular concern in PWS.

Gastroesophageal reflux is a passive phenomenon in which liquid and partially digested food moves up the esophagus from the stomach into the oropharynx. Gastroesophageal reflux is a relatively common finding in otherwise normal (non-PWS) infants, occurring in the majority of infants under 4 months of age<sup>153</sup> and usually resolving within the first year of life.<sup>190</sup> The severity may be increased in infants with hypotonia, prematurity, or other predisposing conditions. Contributory factors may include transient relaxation of the lower esophageal sphincter pressure and positioning after feeds. It has been postulated that reflux may trigger arousal, thereby being protective against sudden death in infants.<sup>190</sup> In addition, in non-PWS infants, it has been found that a nasogastric tube increases the frequency of reflux episodes.<sup>160</sup>

In severe cases, chronic reflux of gastric acid can cause esophagitis, esophageal stricture, and cellular dysplasia and carcinoma of the distal esophagus. In older children and adults, gastroesophageal reflux may be associated with symptoms of “acid reflux” or heartburn. Endoscopic evaluation and surgical treatment may be necessary.

Possible gastroesophageal reflux has been occasionally reported in PWS,<sup>18</sup> but systematic documentation of prevalence has not been performed. Anecdotal experience suggests that clinically significant reflux is not as commonly observed in infants with PWS as might be expected. In addition, typical symptoms and complications due to gastroesophageal reflux have not been reported. This may, in part, be due to the lower volumes per oral feed that are usually ingested by PWS infants.

There are concerns regarding the possibility that due to hypotonia, infants with PWS may be unable to adequately protect the airway during reflux episodes, thereby increasing the risks for aspiration pneumonia and respiratory compromise. As a safety measure, reflux precautions should be taken for all infants with PWS, especially if taking substantial volumes of oral bolus feeds, and continued until the child is ambulatory. Optimal precautions have not, however, been defined in infants with PWS. In non-PWS infants, a 30-degree incline post feeds (e.g., in an infant seat) has been traditionally recommended. Given the concerns that this may worsen reflux in some infants due to increased intra-abdominal pressure, the prone or left-lateral position has been recommended,<sup>160,190</sup> but the relative advantages of this positioning have not been tested in infants with PWS. In any case, a supine position should be avoided.

Gastroesophageal reflux and/or complications related to this condition have not been reported in older individuals with PWS. Since individuals with PWS have decreased pain sensation (see Chapter 5), typical symptoms of heartburn may not be a reliable indicator of acid reflux. In one case of a 27-year-old man with PWS, heartburn was reported, but no abnormalities were noted on endoscopic examination.<sup>204</sup>

Emesis is an active process that may be considered to be a normal protective reflex. When emetic agents and toxins enter the gastrointestinal lumen, mucosal chemoreceptors are triggered which then signal through the vagus nerve back to a brainstem emetic center.<sup>107</sup> Emetic toxins in the bloodstream signal directly to this same area through the area postrema of the brainstem. Processing of these signals results in sequential signaling through vagal and other motor neurons, resulting in retching (simultaneous, forceful contractions of the diaphragm and abdominal muscles) and expulsion (prolonged forceful contraction of the abdominal muscles in coordination with the rib cage and pharyngeal and laryngeal muscles). Retrograde intestinal contraction occurs with gastric relaxation. Emesis then results from sequential and coordinated increases in intra-abdominal and intrathoracic pressure. Active retrograde peristalsis of the stomach or esophagus is not thought to be involved in emesis. Hypothalamic release of vasopressin and oxytocin may also be essential elements of emesis.

A commonly reported feature of PWS is a decreased ability to vomit, with a complete absence of “natural” or induced (e.g., with syrup of ipecac) vomiting noted in a large proportion of individuals.<sup>3,104</sup> The reasons for this are not completely known. Hypotonia of the diaphragmatic, abdominal, and intercostal muscles may be contributory since forceful contractions of these muscles are required for emesis. A deficiency of oxytocin neurons<sup>179</sup> could play a role, although CSF oxytocin levels are reportedly elevated in PWS.<sup>140</sup> Vagal autonomic dysfunction is also a possibility, although, as reviewed in Chapter 5, the evidence for autonomic dysfunction in PWS is limited.

Caution has been advised regarding reliance on emetic agents, particularly syrup of ipecac, in the treatment of accidental poisoning for individuals with PWS since the response may be inadequate. The American Academy of Pediatrics no longer recommends routine supply or use of syrup of ipecac for home treatment of childhood ingestion<sup>46</sup>; therefore, this issue may be a moot point, at least in the U.S. Instead, parents and guardians are advised to call the local poison control center for guidance. However, healthcare practitioners and guardians should be aware of the decreased ability to vomit in the event that an emetic therapy is considered in the emergency room or other medical care facility.

Although most individuals with PWS have a decreased ability to vomit, others may have rumination, a condition characterized by *voluntary* regurgitation of gastric contents that are then rechewed and reswallowed. A survey study found that 10% to 17% of 313 individuals with PWS reported a history of rumination and that approximately half of this group had a history of emesis.<sup>3</sup> Rumination was also suspected

in a 17-year-old who was found to have gastric secretions in her pharynx despite fasting during preparation for general anesthesia.<sup>174</sup> Rumination may be a form of self-stimulation and, in the case of PWS, a means of obtaining food, albeit reprocessed.

Regurgitated food usually contains gastric acid, which may add to problems with dental enamel erosion. Therefore, in addition to behavioral treatment, the use of pharmacologic agents to block stomach acid secretion should be considered in patients who have rumination.

*Gastric Dilatation:* In 1997, Wharton et al.<sup>197</sup> reported six females with massive gastric dilatation; two died of gastric necrosis, one died of cardiac arrest, and three survived. Fever, abdominal pain, and distention were presenting signs, and vomiting was reported in two cases. These individuals had all had strict dietary control; the authors postulated that gastric muscular atony and atrophy may have occurred as a result of the dietary limitations, resulting in dilatation and necrosis following sudden ingestion of a large quantity of food. No additional cases have been published and the prevalence of this condition in PWS is unknown. However, aside from the usual recommendations for prevention of binge eating, caretakers should be vigilant for signs of acute onset of unusual abdominal distention, fever, and emesis.

*Bowel Complaints:* As indicated in Figure 6.2, complaints related to bowel function are frequently reported by individuals with PWS (data summarized from various sources). For the most part, these appear to

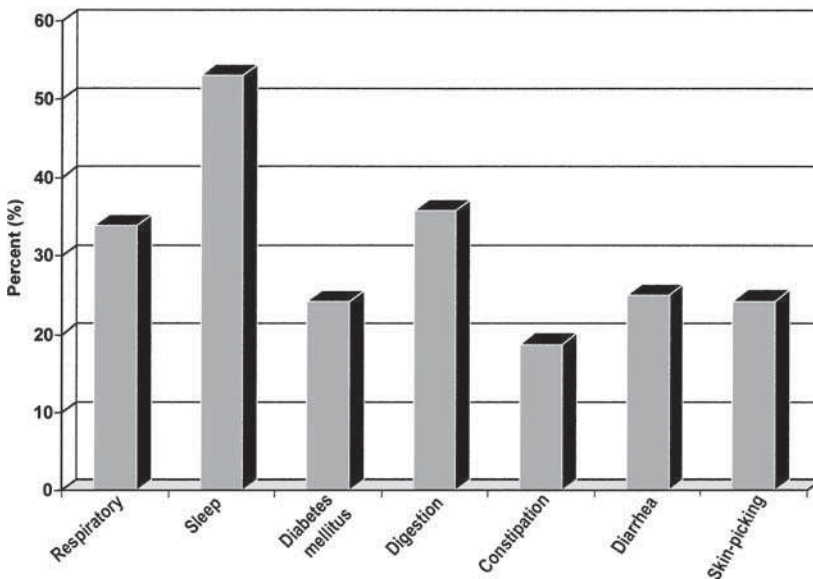


**Figure 6.2.** Symptom prevalence in adults with PWS (Sources: Butler et al.,<sup>27</sup> 2002, Holm et al.,<sup>104</sup> 1992, and personal communications from S.B. Cassidy and B.Y. Whitman.)

be secondary to factors related to eating. As of this writing, no intrinsic abnormalities in bowel anatomy or function have been associated with PWS.

Composite data indicate that 20% of individuals with PWS report constipation. Constipation can be defined as hard, dry bowel movements, usually occurring less than three times a week. Abdominal and rectal pain, rectal fissures, hemorrhoids, and rectal bleeding (bright red blood) may occur in association with the disordered defecation. In addition, affected individuals may have abdominal distention, bloating, and a general feeling of discomfort. Lack of dietary fiber and inadequate liquid ingestion may be contributory factors. Hypotonia of the pelvic floor and abdominal muscles can increase the difficulty of defecation. General physical immobility is also associated with constipation. Although hypothyroidism does not occur with increased frequency in PWS, it is fairly common in the general population and often presents with constipation.

Treatment of constipation involves provision of adequate dietary water and fiber, encouragement of physical activity, and thyroid hormone replacement, if deficient. In some cases, rectal stimulation, irrigation, suppositories, or enemas may be necessary to clear the rectal ampulla. Laxatives may be helpful in some cases; however, chronic use is not recommended.

Diarrhea, often thought of as the opposite of constipation, can be defined as loose, watery, and frequent stools. Diarrhea is reported somewhat more frequently than constipation in PWS. Noninfectious diarrhea can be caused by consumption of large amounts of poorly absorbed dietary sweeteners (e.g., sorbitol or fructose) or fat substitutes (olestra), use of antiabsorptive agents (e.g., orlistat), and food intolerance (e.g., lactose intolerance). Consumption of contaminated foods, not uncommon in PWS due to the foraging behavior, enhances the likelihood of acquiring infectious diarrhea. A careful history, examination of the stool and blood count, stool cultures (including cultures for *C. difficile*, if indicated), and parasite studies (including *giardia lamblia*) may be included in the evaluation.

Treatment of diarrhea is dependent upon the cause. Diarrhea, especially if copious, watery, and acidic, can cause perianal irritation, bleeding, and infection. These secondary conditions also require attention and treatment.

Rectal ulcers may occur as a result of a regional skin picking sometimes termed "rectal digging."<sup>14,38,143</sup> This behavior is often exacerbated by rectal irritation from constipation, diarrhea, or large stools. Symptoms may include mucoid rectal discharge, bloody stools, constipation, rectal pain, abdominal pain, and tenesmus. Behavioral and possibly psychotropic agent therapies are the recommended therapy for skin picking (see Chapter 12). Stool softeners and treatment of constipation and other contributory factors are also necessary to avoid further rectal irritation.

Treatment of bowel disorders in individuals with PWS often requires ongoing specialized treatment and monitoring. A multidisciplinary approach is often necessary to optimize therapy.

## Other Gastrointestinal Organs

No intrinsic structural or functional abnormalities in pancreatic exocrine or endocrine function have been identified in PWS. Disordered serum levels of pancreatic secretions (e.g., insulin, pancreatic polypeptide) have been reported, as discussed elsewhere, but are not postulated to be due to primary pancreatic disease.

Nonalcoholic fatty liver disease (NAFLD) is a condition that typically occurs in obese individuals, particularly those with insulin resistance, characterized by lipid accumulation in the liver.<sup>67</sup> NAFLD may progress through the stages of fat accumulation (steatosis), fibrosis and inflammatory necrosis (nonalcoholic steatohepatitis), cirrhosis, and liver failure. The first stage is fairly common in the general obese population; subsequent progression is less common, but NAFLD is a major cause of nonalcoholic liver failure in the overall population. Diagnostic signs include elevated liver enzymes, liver enlargement, and ultrasound evidence of steatosis. Hepatic steatosis has been occasionally reported in cases of PWS,<sup>99,203</sup> but the overall frequency is not known. The treatment of NAFLD has not yet been delineated, although metformin may have beneficial effects in the early stages of disease.<sup>112</sup>

There are two case reports of childhood liver tumor in PWS, an adenoma and a hepatoblastoma.<sup>95,180</sup> It is not known whether these were specific or chance associations.

## Obesity and Nutrition

### Definitions

Obesity or overweight is both a major feature of PWS and a burgeoning problem in the non-PWS population. However, the recognition, diagnosis, and characteristics of obesity in PWS are very different from virtually every other population. In addition, while the terms *obesity* and *overweight* may be interchangeable in the general population, this may not be the case in PWS. This is not merely a semantic argument; distinguishing obesity from overweight may have important pathophysiologic and treatment implications for PWS.

The derivation of the word obesity is somewhat obscure. An online dictionary of etymology ([www.etymonline.com](http://www.etymonline.com)) has the following listing:

**obesity**—1611, from Fr. *obésité*, from L. *obesitas* "fatness, corpulence," from *obesus* "that has eaten itself fat," pp. of *obdere* "to eat all over, devour," from *ob* "over" + *edere* "eat." The adj. *obese* is attested from 1651.

Other sources trace the word to *ob* (Eng: toward) *ese* (Ger: eating).

In modern medical terminology, obesity is often defined as a condition characterized by excessive body fat. While some definitions include reference to overweight resulting from excess body fat, a more standard scientific definition refers to an excess proportion of fat to nonfat mass. This latter definition is probably most relevant to PWS.

In normal human physiology and with usual diet composition, as weight is gained, fat and nonfat (bone, muscle, water) mass increase in a nearly linear relationship, with fat increasing at a faster rate than nonfat mass.<sup>75</sup> This “companionship of lean and fat”<sup>75</sup> holds for a variety of human conditions in which total body weight is altered, including diabetes mellitus, anorexia nervosa, and “normal” obesity. In an underweight individual, there is a relatively higher proportion of lean mass. As body weight increases, the ratio of fat to nonfat mass gradually increases, but both compartments increase in a linearly correlated fashion.

Because of this relationship, a ratio of weight to height provides a reasonable estimate of total body fat, with weight (kg) divided by height squared ( $m^2$ ), also known as body mass index (BMI), providing the best approximation of more direct measures of body fat (see Body Composition section in this chapter). For non-PWS populations, BMI provides a convenient noninvasive indicator of body fat. As defined by the Centers for Disease Control, obesity in adults is equated with a BMI of  $\geq 25$ . However, it is possible to have a BMI in the obese range without actually being obese, as in the case of a body builder who has increased muscle mass.

Since the proportions of body fat to height change during human growth, childhood *overweight* is defined as a BMI  $\geq 95$ th percentile as compared with the age-/sex-related norms; *obesity* is not defined by BMI alone. As with adults, overweight usually but not always equates with obesity. For instance, athletic adolescent males may have increased muscle mass, decreased fat mass, and a relatively high BMI.

PWS is one of the few conditions in which the companionship between fat and lean does not hold. Forbes noted that while individuals with a number of conditions showed a linear, superimposable relationship of lean mass and weight, individuals with PWS were clear outliers, with a marked deficit in lean mass for weight.<sup>75,76</sup> Other studies have shown an excess of body fat in individuals with PWS, including underweight infants.<sup>20,40,54,55</sup>

Therefore, in the natural history of PWS, while overweight invariably equates to obesity, normal and underweight are also accompanied by increased body fat. At least by the definition of increased fat to lean, all individuals with PWS, regardless of weight, may be considered obese. Distinction of obesity and overweight (total body mass) may be important in terms of defining related morbidity risks and treatment. In addition, total fat mass and fat distribution may have different pathophysiologic implications from obesity and overweight.

### Pathogenesis

Given the above discussion, the pathogenesis of the increased fat mass in PWS can be separated into two considerations, which may or may not be related to one another:

1. What causes the apparent violation of the “companionship rule”; i.e., why does fat mass increase in an abnormal proportion to lean mass as weight increases?



2. What causes the apparently insatiable appetite and the consequent unlimited weight (primarily fat) gain?

Knowledge of the pathogenesis of these conditions could be crucial to designing adequate treatment protocols.

The inappropriate proportion of fat to nonfat mass probably begins *in utero* and is accompanied by an absolute deficit in muscle and bone mass. This could result from either (1) inappropriate preferential shuttling of nutrients into fat, thereby causing a deficit in lean (bone and muscle) mass, and/or (2) inappropriately low utilization of nutrients by bone and/or muscle, leading to a default deposition of fat.

The mechanisms by which the human body normally shuttles ingested substrate (glucose, amino acids, fatty acids) into fat, muscle, and bone have not been completely defined<sup>72,98,115</sup> and a discussion of this topic is beyond the scope of this chapter. There is evidence that hormones and neuropeptides that may regulate appetite (e.g., leptin, neuropeptide-Y (NPY), adiponectin, Agouti-related protein) may also affect substrate partitioning<sup>98,115</sup>; however, much of the data has been collected in rodents and may not apply directly to humans. In addition, no specific defects in the physiology or action of these substances have been reported in PWS, and none are coded within the PWS gene region. Therefore, it is not known at this time whether the primary body composition abnormality in PWS is excess lipogenesis, decreased formation of muscle and/or bone, or a concomitant dysregulation of both fat and nonfat mass accretion.

The propensity for insatiable appetite and weight gain in PWS is likewise not completely understood. Normal eating behavior has been separated into three components: (1) an initial, relatively acute “drive to eat,” or *hunger*; (2) an immediate postmeal feeling of fullness, or *satiety*; and (3) a longer-lasting feeling of satisfaction, or *satiation*. The control mechanisms for each of these stages are likely to be different. On a theoretical basis, environmental stimuli and voluntary control are more likely to influence hunger, whereas satiety and satiation may be more dependent on intrinsic physiologic control. Studies indicate that the primary deficit in PWS involves the third stage, satiation.<sup>131</sup>

Satiation may be controlled by endogenous appetite suppressants and stimulants (orexins). Theoretically, the balance between these two components is maintained by peripheral metabolic and/or neurogenic signals. Many of the characterized appetite-regulatory pathways in rodents and humans have been localized to the arcuate nucleus of the hypothalamus. A primary hypothalamic defect has been postulated to drive the hyperphagia in PWS, although no relevant functional or structural abnormalities have been identified thus far.<sup>81,82,85,86</sup> The possibility exists that the primary disorder may involve a defect in peripheral satiety signaling, perhaps related to the defective nutrient cycling and body composition abnormality. This latter model would agree with the clinical observation that the eating behavior in PWS more closely resembles nutritional deprivation or starvation rather than normal hunger.<sup>103,127</sup>

As of this writing, the study of appetite regulatory peptides in the general population and in PWS is actively developing.<sup>50,56,199,201</sup> The following list summarizes current knowledge of several postulated appetite regulatory peptides in relation to PWS. In general, the current model of appetite regulation includes peptides generated within the gastrointestinal system or body tissues that are released into the bloodstream (endocrine) or nervous system (neurocrine). These peptides then feed back to specific receptors in the hypothalamus, resulting in generation of signaling within the central nervous system and back to the body tissues.

### 1. Cholecystokinin (CCK)

CCK is produced by the endocrine I cells in the duodenum and jejunum in response to fat, amino acids, and gastric acid. Actions include stimulation of pancreatic enzyme secretion, gallbladder contraction, intestinal motility, insulin secretion, and pancreatic polypeptide secretion. CCK delays gastric emptying and inhibits release of gastric acid. In the brain, high concentrations of CCK are present in the cerebral cortex. CCK is postulated to be responsible for initiating satiety during a meal.<sup>201</sup> In PWS, fasting levels of CCK are normal but unlike in non-PWS controls, fasting CCK is not correlated with free fatty acid levels.<sup>31</sup> In response to a protein meal, CCK levels rise normally in individuals with PWS.<sup>183</sup>

### 2. Pancreatic Polypeptides

The pancreatic polypeptides PP, PYY (peptide YY), and NPY (neuropeptide Y) are produced in the pancreatic islets of Langerhans (PP), the large and small bowel (PYY), and peptidergic neurons of the stomach, small intestine, and central nervous system (NPY). PP secretion is primarily stimulated by protein intake and cholinergic activity. PYY secretion is stimulated by mixed meals and oleic acid. NPY functions as a neurotransmitter, with high concentrations in the arcuate nucleus of the hypothalamus. PP and PYY are postulated to play a role in satiety.

PP secretion in response to a protein meal has been reported to be deficient in PWS.<sup>183,209,210</sup> Short-term infusion of PP was initially reported to cause a mild inhibition of food intake in females with PWS<sup>13</sup>; however, a more detailed investigation indicated no effect.<sup>208</sup>

PYY levels have been reported to be low in non-PWS obese individuals, and PYY infusion causes a reduction in food intake.<sup>9</sup> PYY levels are reportedly low in PWS<sup>29</sup>; however, infusion studies have not been reported.

NPY activity in the hypothalamus is postulated to stimulate food intake.<sup>199</sup> Hypothalamic NPY neurons appear to be normal in PWS.<sup>85</sup> Serum levels of NPY are reported to be low-normal in adults with PWS and do not change with GH therapy.<sup>108,109</sup>

### 3. Hypocretins (orexins)

Hypocretins are neurocrine peptides that are postulated to stimulate feeding. Hypocretin-containing neurons in the lateral hypothalamus

are stimulated in response to hypoglycemia. Hypocretins are also postulated to play roles in regulating energy expenditure and sleep/wake cycles. In a study of hypocretin levels in relation to sleep disorders,<sup>142</sup> cerebrospinal fluid hypocretin levels were found to be normal in a 16-year-old with PWS. However, cerebrospinal fluid hypocretin levels were reported to be low in four patients with PWS, in association with daytime sleepiness.<sup>154</sup>

#### 4. Agouti-Related Protein (AGRP)

AGRP production is co-localized with NPY in the hypothalamus. AGRP stimulates food intake by inhibiting the actions of melanocortin, an anorexigenic neurocrine peptide. AGRP expression was reported to be decreased in the neonatal mouse model of PWS, in which there is failure to gain weight (as with human PWS).<sup>80</sup> However, AGRP neurons appear to be normal in older individuals with PWS.<sup>85</sup>

#### 5. Ghrelin

Ghrelin is a peptide released from cells in the stomach. The normal function of ghrelin is not completely defined. In both rodents and humans, serum ghrelin levels rise progressively during fasting and it is postulated that ghrelin provides a signal to initiate food intake. In agreement with this theory, pharmacologic administration of ghrelin to mice results in increased food intake. However, the ghrelin knockout (deficient) mouse has no apparent defect in appetite or any other body function.<sup>178</sup> Recent studies indicate that the hyperphagic effect of exogenously administered ghrelin in mice is mediated by NPY/AGRP neurons.<sup>44</sup>

Serum ghrelin levels have been reported to be elevated in individuals with PWS<sup>29,48,51,84,92,109</sup> and are postulated to contribute to the hyperphagia. However, examination of the data reveals that levels are not increased in all individuals with PWS (although hyperphagia is virtually universal) and mean levels are not significantly different from normal in some studies.<sup>16</sup> In addition, serum ghrelin levels appear to decrease appropriately in response to meals and somatostatin administration in PWS.<sup>16,93</sup> Therefore, as of this writing, the role of ghrelin in PWS pathophysiology is not known.

#### 6. Opioids (endorphins)

Opioid peptides produced within the central nervous system function as neurotransmitters. In some cases, opioids may enhance intake of foods, particularly sugary foods, perhaps by inducing positive sensations.<sup>199</sup> Opioids have been postulated to play a role in various types of eating disorders, including PWS.<sup>116</sup> However, serum levels of beta-endorphin were found to be normal in children with PWS,<sup>138</sup> and administration of opioid inhibitors had no effect on food intake.<sup>207,211</sup>

#### 7. Leptin

Leptin is produced by fat and appears to signal adequacy of energy storage back to the brain.<sup>26,37,39,41,132</sup> Except in those conditions involving genetic defects in leptin or leptin receptor expression, serum leptin

levels correlate directly with body fat.<sup>202</sup> In cases of genetic defects in leptin synthesis, the hyperphagia and other physiologic abnormalities are alleviated by leptin administration. However, it is not clear at this point whether pharmacologic administration of leptin to normal obese individuals, who have high leptin levels, will lead to significantly decreased food intake. It has been postulated that leptin functions primarily to signal energy deficiency rather than adequacy.

In PWS, leptin levels are increased and appear to be directly correlated with body fat.<sup>26,37,39,158</sup> Molecular defects of the leptin gene have not been identified in PWS.<sup>33</sup> Growth hormone therapy may decrease leptin levels in PWS; this effect is probably related to decreased absolute body fat.<sup>59,111,148,205</sup>

### ***Energy Expenditure***

Previous studies have described alterations in metabolic rate in individuals with PWS. Schoeller et al.<sup>169</sup> noted problems with use of common mathematical formulae to predict the basal metabolic rate (BMR) in adults with PWS and advocated use of the Cunningham BMR formula to adjust for the deficit in lean mass (FFM). Subsequent studies<sup>100,188</sup> have demonstrated a low basal metabolic rate with varied interpretation of data dependent upon the technique of body composition analysis. However, although resting energy expenditure may be normal or near-normal for lean mass, lean mass is deficient, leading to deficient expenditure for total body mass.<sup>12,82,169</sup>

Despite differences in body composition, energy expenditure during physical activity is similar to that of controls<sup>151,152</sup> when corrected for lean mass. However, individuals with PWS are less active than controls.<sup>49,189</sup> The combination of diminished BMR and activity level necessitates lower caloric intake or a significant increase in physical activity to avoid excessive weight gain.

### **Associated Morbidities**

Body fat itself is rarely a direct cause of morbidity or mortality. Fat embolism is an example of direct fat-related morbidity, but this condition is not reported to occur with increased frequency in PWS. In PWS, the increased *proportion* of fat to lean mass (regardless of weight) is largely the result of decreased muscle mass. The resultant hypotonia is a major contributor to morbidity and mortality, as discussed in previous sections. As body weight increases above normal in PWS, the fat mass itself becomes problematic.

Body fat can contribute indirectly to pathophysiology in two ways: (1) complications due to a mass effect, i.e., in morbidly obese individuals, and (2) via metabolic complications related to fat.

The detrimental effects of excess body mass are well recognized. In particular, increased fat is associated with respiratory impairment and obstructive apnea. The sheer weight of excess fat in the presence of low muscle mass also contributes to impaired physical mobility and difficulty with daily tasks. Many adults with PWS adopt a typical hypotonic posturing, with both arms folded across the upper abdomen,

while others become wheelchair-dependent in young adult life. Increased fat mass may also theoretically exacerbate scoliosis and fragility fractures involving weight-bearing bones and joints (vertebrae and hips), but, on the other hand, increased weight may augment bone mineral density, as shown in non-PWS populations.<sup>129</sup>

Metabolic effects of increased body fat have been well defined in the general population. In non-PWS children, early puberty (particularly adrenarche),<sup>163</sup> accelerated linear growth, and advanced bone age can occur; final adult height is usually not adversely affected despite the accelerated physical development. Adrenarche is the portion of sexual development characterized by increased production of adrenal androgen precursors, which, in the peripheral tissues, are converted to testosterone and dihydrotestosterone. In normal puberty, adrenarche is responsible for secondary sexual hair growth in females; the effect of adrenarche is usually less notable in boys due to testicular production of testosterone. The hormones produced during adrenarche also cause acceleration of bone growth and epiphyseal closure. The physiologic control of the timing of adrenarche has not been defined; however, insulin resistance and hyperinsulinemia are associated with earlier onset.

In children with PWS, premature adrenarche occurs in a relatively small subset of cases<sup>121,126,167</sup> and is manifested by early (before age 8 to 9 years) appearance of pubic hair. Anecdotal experience suggests that the frequency of premature adrenarche is less than might be expected in a similarly overweight non-PWS population. In affected children, the increased linear growth rate due to adrenarche often replicates a normal, non-PWS growth rate (which is actually accelerated for PWS). Unfortunately, the end result is often extreme short stature due to premature epiphyseal closure, which is quite different from the normal stature attained by non-PWS children with obesity-related premature adrenarche. Therefore, “idiopathic” premature adrenarche cannot be considered to be a benign condition in PWS.

In older children, adolescents, and adults, obesity can lead to metabolic syndrome, also known as dysmetabolic or insulin-resistance syndrome (defined by various criteria, but generally including insulin resistance, overweight/obesity, dyslipidemia, and hypertension; all associated with increased cardiovascular risk), polycystic ovary syndrome, and Type 2 diabetes mellitus.<sup>58</sup> In non-PWS populations, insulin resistance and consequent morbidities have been specifically associated with increased abdominal visceral fat (as opposed to subcutaneous fat).

Glucose intolerance and Type 2 (also known as non-insulin-dependent) diabetes mellitus (T2DM) can occur in patients with PWS.<sup>27,42,78,91,113,123,150,162,170,172,203</sup> The usual case of T2DM in PWS is indistinguishable from non-PWS obesity-related diabetes, which is occurring with increasing frequency worldwide.<sup>198</sup> Unlike Down and Turner syndromes, there does not appear to be any unique risk for Type 1 (insulin-dependent) diabetes mellitus (T1DM) in PWS. In addition, no specific metabolic abnormalities have been identified in PWS to

suggest a unique predisposition to T2DM except for obesity.<sup>21,136</sup> A reduced amount of insulin receptors was noted in one report, but the clinical significance of this finding is uncertain.<sup>120</sup>

Recent data indicate that individuals with PWS may have a lower risk for insulin resistance and T2DM than would be expected based on the degree of overweight. Average fasting insulin levels are reported to be low in children and adults with PWS and there is a relative lack of clinical signs consistent with insulin resistance,<sup>57,111,145,156,181,206</sup> although some reports have found elevated fasting insulin,<sup>125,155</sup> and others have reported elevated fasting but decreased 2-hour postprandial insulin.<sup>128</sup> However, the bulk of evidence suggests that insulin levels are relatively low in most individuals with PWS, arguing against an increased frequency of insulin resistance. In addition, serum levels of adiponectin, a protein secreted by adipocytes that is thought to increase insulin sensitivity, are unexpectedly high in PWS,<sup>110</sup> whereas low levels are usually observed in non-PWS patients with obesity and insulin resistance.

In non-PWS individuals, insulin resistance syndromes and T2DM are part of a spectrum of disorders related to increased body fat and, in particular, intra-abdominal visceral fat<sup>73,165</sup> (as distinguished from subcutaneous fat). Lipid deposition in muscle and other body tissues may also be contributory.<sup>114</sup> However, in obese individuals with PWS, subcutaneous but not visceral fat has been found to be increased<sup>83,182</sup>; the mechanisms for this occurrence have not been defined. In addition, visceral fat characteristics for individuals with PWS and insulin resistance have not yet been reported.

Monitoring for signs and symptoms of insulin resistance and T2DM should be a routine element of care for all individuals with PWS. Some cases of T2DM may present with the classic symptoms of diabetes mellitus: polyuria, polydipsia, and, in some cases, unexpected weight loss despite continued hyperphagia. Ketoacidosis, obtundation, and disordered consciousness may occur in the most severe cases.<sup>203</sup> However, most individuals with insulin resistance or T2DM will be asymptomatic. A classic, but not universal, physical sign of insulin resistance is acanthosis nigricans: hyperpigmented, velvet-textured skin in the nuchal, axillary, inguinal, and other folds of the body thought to be due to direct or indirect effects of hyperinsulinemia on keratinocytes.<sup>184</sup>

Individuals suspected of having insulin resistance should be screened for associated morbidities, including dyslipidemia (fasting lipid panel) and hypertension. Diagnosis of impaired glucose tolerance (IGT) and T2DM should be made according to criteria of the American Diabetes Association<sup>2</sup>:

1. Symptoms of diabetes plus casual plasma glucose concentration  $\geq 200$  mg/dl (11.1 mmol/l). Casual is defined as any time of day without regard to time since last meal. The classic symptoms of diabetes include polyuria, polydipsia, and unexplained weight loss.

or



2. FPG  $\geq 126$  mg/dl (7.0 mmol/l). Fasting is defined as no caloric intake for at least 8 hours.

or

3. Two-hour post-load glucose  $\geq 200$  mg/dl (11.1 mmol/l) during an OGTT. The test should be performed as described by the World Health Organization (WHO), using a glucose load containing the equivalent of 75-g anhydrous glucose dissolved in water.

Since criteria 1 and 3 do not require an elevated fasting glucose, and a 2-hour oral glucose tolerance test may not always be feasible, some practitioners utilize a random glycated hemoglobin or hemoglobin A1c measurement to screen for clinically significant glucose intolerance and diabetes mellitus.

### Treatment

Nutritional management of PWS can be separated into four major areas of concern:

1. Control of under- and overweight
2. Optimization and conservation of lean mass
3. Special nutritional considerations
4. Treatment of obesity-related morbidities

Evolving clinical needs for the individual with PWS requires adaptation of nutritional support. During infancy, diminished muscle tone affects the volume of caloric intake during feedings. A variety of techniques are available for nutritional support of the infant with PWS including adaptive feeding bottles and nipples (e.g., Haberman feeder, cleft palate nurser, adaptive nipples), thickening agents (Thick-It, cereal), formula concentration, and nasogastric tubes. The feeding therapy utilized is determined by the adequacy of swallowing skills, and nutritional status.

Nasogastric and gastrostomy feedings are commonly used to meet the nutritional needs of infants with PWS. Gavranich et al.,<sup>79</sup> reported use of tube feedings for a mean of 8.6 weeks among 67% of infants with PWS in New South Wales. Since gastrointestinal absorption and motility are essentially normal, intravenous total parenteral nutrition is usually not required. In infants receiving feedings primarily through a non-oral route, oral feedings as tolerated and non-nutritive sucking should be continued to encourage development of oromotor strength and coordination.

Intake parameters during infancy can be patterned along guidelines from the Nutrition Committee of the American Academy of Pediatrics.<sup>47</sup> During the first 6 months of life, breast milk and infant formula should serve as the primary nutritional source and should be given in usual amounts. Solids are generally introduced at 5 to 6 months of age and advanced in texture, dependent upon oral motor skills. Higher-calorie solids, desserts, and juices are commonly avoided. Through close monitoring of growth data over the first 2 years, oral intake can be appropriately adjusted to maintain weight for height between the

25th and 80th percentiles. Caloric restriction under the guidance of an experienced nutritionist or other health care provider is required, with supplementation of deficient vitamins and minerals, if weight gain becomes excessive.

Nutritional strategies beyond the toddler years focus on avoidance of overweight. Limited studies<sup>106,159</sup> have evaluated the caloric requirements for individuals with PWS. Weight maintenance has been reported with intakes of 8 to 11 kcal/cm/day (non-PWS children require 11–14 kcal/cm/day; cm = height); weight loss has been documented with intakes of 7 kcal/cm/day. Sample calorie guidelines, adapted from guidelines published by PWSA (USA)<sup>17</sup> are listed in Table 6.1. It should be noted that while these guidelines are based on logical criteria, there are no prospective data regarding efficacy. In addition, these guidelines may be excessive for children who are unusually inactive and, conversely, inadequate for children with PWS receiving growth hormone therapy.

Similar guidelines have not been specifically formulated for adolescents and adults with PWS, although a general recommendation has been 800 to 1,000 kcal/day for weight loss. These calorie guidelines are a significant reduction from usual food intake in the general population; therefore, the individual with PWS will probably need to have different food preparation and provision from the rest of the household.

A typical approach to a calorie-restricted weight control treatment plan is to introduce a “balanced” calorie reduction, with maintenance of the usual carbohydrate-protein-fat proportions (i.e., 60%-15%-25%, respectively). Emphasis on low-glycemic-index carbohydrates (i.e., slowly-absorbed complex carbohydrates rather than, for instance, high sugar foods) may also reduce insulin secretion, facilitate optimal nutrient utilization and have a positive effect on satiety,<sup>135</sup> although these effects have not been studied in individuals with PWS.

Adherence to a calorie-restricted diet requires intensive and continuous monitoring of intake and regular dietary counseling, including analysis of food histories and attention to possible associated nutrient

Table 6.1. Sample Calorie Guidelines

| Age (yr) | Average Height (cm) | Weight Maintenance (kcal/d) | Weight Loss (kcal/d) |
|----------|---------------------|-----------------------------|----------------------|
| Female   |                     |                             |                      |
| 3        | 89                  | 700–980                     | 630                  |
| 5        | 102                 | 800–1120                    | 720                  |
| 7        | 112                 | 880–1232                    | 790                  |
| 9        | 135                 | 1060–1484                   | 954                  |
| Male     |                     |                             |                      |
| 3        | 94                  | 740–1036                    | 660                  |
| 5        | 107                 | 840–1176                    | 760                  |
| 7        | 119                 | 940–1316                    | 845                  |
| 9        | 122                 | 960–1344                    | 864                  |

deficiencies. Behavioral aspects of this plan require attention to all potential sources for intake including cafeterias, school buses, classroom activities ("life skills"), vending machine access, neighbors, and convenience stores as well as home access (e.g., pantry, garbage cans, refrigerator, tabletop). Locks on kitchen doors and refrigerators are often recommended elements of this plan. More detailed discussions of behavioral and environmental management strategies appear elsewhere (see Chapters 12 and 18).

There is no doubt that total calorie restriction will achieve weight maintenance or loss if completely implemented; however, it remains unresolved as to whether this approach is justified in view of the physiology. As mentioned above, there is growing consensus that the food foraging and apparently insatiable appetite in PWS may be triggered by internal mechanisms that more closely resemble true starvation than non-PWS pre-meal hunger or eating behavior. If this is true, then the intentional restriction of all intake could have detrimental effects on overall behavior and well-being and may, in fact, augment foraging and food-sneaking behavior. This hypothesis has not been tested, although it appears to hold some validity on review of anecdotal patient experience.

An equally important issue relates to adverse effects on body composition. Although increased body fat and overweight is a major visible morbidity in PWS, a more crucial functional morbidity is the lack of lean mass. In non-PWS individuals, induction of an energy deficit (e.g., fasting, total calorie restriction) and weight loss using a balanced nutrient intake results in loss of not only fat mass, but also lean mass. In addition, the lower the total calorie intake, the higher the proportion of lean mass lost. In non-PWS individuals, excess body fat will provide a relative protection against loss of lean mass (i.e., thinner individuals lose proportionately more lean mass than obese individuals during weight loss).<sup>77</sup>

As stated by Dr. Gilbert Forbes, a pioneer in this field of research, "There is no level of reduced energy intake that will completely spare LBM [lean body mass] when significant amounts of body weight are lost."<sup>75</sup> In individuals with PWS, where total lean mass is deficient even in the presence of overweight, there is no reason to suspect that a balanced calorie restriction diet will result in preservation of absolute lean mass.

However, lean mass can be at least relatively preserved during calorie deficit by preferentially preserving protein intake. The initial observations of this phenomenon preceded the currently popular low-carbohydrate, increased protein diets.<sup>75</sup> In a short-term metabolic unit study in four patients with PWS, a protein-sparing (1.5 gm of meat protein per kg body weight), ketogenic, modified fast preserved positive nitrogen balance and lean body mass in the presence of significant weight reduction.<sup>15</sup> A similar nutritional approach in an obese ventilator-dependent adolescent with PWS apparently facilitated weight management and weaning from the ventilator.<sup>45</sup>

In addition to potential effects on preservation of lean mass, protein may have a greater positive effect on satiety than carbohydrates or fat,

as demonstrated in both short- and long-term human studies.<sup>5,25</sup> Although this effect has not been investigated in individuals with PWS, it was postulated to occur in outpatient follow-up of patients involved in the previously mentioned study using a protein-sparing fast.<sup>15</sup>

A ketogenic protein-sparing fast is probably not practical for most individuals with PWS. However, several other approaches to high-protein, lower carbohydrate meal planning are available. Popular diets using this approach typically result in 28% to 35% calories from protein, 8% to 40% from carbohydrate, and the remainder from fat.<sup>5</sup> One of the authors (PDKL) has prescribed modified lower-carbohydrate, lower-fat guidelines in his PWS clinics for several years, an approach which is similar to other, perhaps more stringent regimens.<sup>5,146,147</sup> The basic five-step approach is as follows: (1) elimination of sugar and all packaged foods containing >5 g sugar per serving, (2) limitation of complex carbohydrates to one to two servings three times daily, with one serving = 15 gm of carbohydrate, (3) avoidance of fried and fatty foods, (4) encouragement of lean protein intake, and (5) provision of “free foods”—i.e., carb-free, low-fat, low-calorie—for ad lib snacking and/or foraging. In addition, an exercise guideline of 30 minutes sustained activity, three to five times weekly is recommended. This regimen is provided as a one-page guideline and reviewed during clinic visits. For most individuals, adherence to this simple plan results in a substantial reduction in total calories. This approach has the advantages of being easy to learn (requires teaching of food label readings and basic carbohydrate counting), relatively straightforward implementation, and possible integration into usual household eating patterns. More structured dietary regimens can be added to this basic program for individual patients.

Whatever dietary approach to weight control is taken, it is important that it be logical, consistent, easily implemented, emphasized at each clinic visit, and carefully monitored. Modifications should be made for individual patients, and in children developmental changes should be taken into account.

Pharmacologic agents for weight management should be considered as adjuncts and not primary treatment modalities. None of the appetite suppressant or antiabsorptive agents marketed for obesity treatment have shown efficacy in PWS, and systematic studies have not been published. Some of the psychotropic agents commonly used in PWS have been anecdotally reported to control food-foraging behavior, but exacerbation of overeating has also been observed.<sup>118</sup> Anecdotal reports indicate that growth hormone therapy may have a beneficial effect on eating behavior, but this has not been demonstrable in objective studies. In a short-term uncontrolled trial, the anti-epileptic medication, topiramate, was reported to improve eating and other behaviors in seven patients with PWS, resulting in weight loss in three<sup>175</sup>; however, several of the subjects were on concomitant medications and the overall results were not entirely conclusive.

Personal experience and one report<sup>42</sup> indicate that metformin may have efficacy for weight control in PWS when coupled with dietary management, particularly with carbohydrate limitation. Similar results

have been reported in treatment of non-PWS obesity.<sup>6,146,147</sup> The mechanism(s) of action for metformin in weight management have not been completely elucidated, although an anorectic effect has been demonstrated in animal studies.<sup>112</sup>

Surgical options for weight management are not generally recommended in PWS. Bariatric surgery causes weight loss through either a diminished capacity for food intake and/or via reduced digestion and absorption of food. In non-PWS obesity, studies in adolescents and adults show efficacy in promoting weight loss, although surgical risks, gastrointestinal problems, and malabsorption are a concern.<sup>71</sup>

Experience with bariatric surgery in PWS has been less encouraging, as summarized in Table 6.2, although relatively long-term success has been reported in selected patients.

There is no apparent effect of bariatric surgery on hyperphagia in PWS. Therefore, the need for dietary intervention and monitoring is not eliminated. Over the long-term, weight gain may recur after the patient develops compensatory dietary strategies. At the current time, bariatric surgery should be considered only in severe cases in which serious obesity-related morbidities are present and rapid weight loss is considered to be potentially beneficial.

### Special Nutritional Considerations

Vitamin and mineral supplementation is highly recommended for individuals with PWS and particularly for those on a balanced, calorie-restriction diet. For example, the sample calorie guidelines from PWSA (USA)<sup>17</sup> listed in Table 6.1 are deficient in calcium, iron, vitamin D, vitamin E, biotin, pantothenic acid, magnesium, zinc, and copper; multivitamin and mineral supplementation is recommended in the publication. In addition, many individuals with PWS have limited sun exposure, especially those affected with hypopigmentation. Since a large proportion of the body stores of vitamin D are synthesized in response to sunlight, lack of sun exposure can result in vitamin D deficiency and an increased risk for osteoporosis.

As a general rule, it is recommended that all patients with PWS receive daily multivitamin and mineral supplementation in consideration of their individualized meal plan and sun exposure. An over-the-counter preparation may be adequate for many patients. Others may require additional monitored supplementation with calcium, trace minerals, and vitamins. Trace mineral, iron, and fat-soluble vitamin supplementation should be carefully monitored to avoid overload.

### Obesity-Related Morbidities

#### *Premature Adrenarche*

In children without PWS, premature adrenarche is usually a benign condition that does not require specific therapy; indeed, specific therapies have not been proven to have efficacy.<sup>163</sup> In some cases, premature adrenarche may be associated with early central puberty, which may require treatment. As mentioned previously, premature adrenarche in

Table 6.2. Bariatric Surgery in Prader-Willi Syndrome

| Reference                                   | Type of Surgery                       | No. of Patients | Median Age | Median Weight | Success Rate                                                             | Complications                                                                                                                                                                                                    |
|---------------------------------------------|---------------------------------------|-----------------|------------|---------------|--------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Soper et al. (1975) <sup>176</sup>          | Gastroplasty                          | 7               | 15 yrs     | 92.5 kg       | 43%?                                                                     | 57% required revisions due to inadequate weight (wt) loss                                                                                                                                                        |
| Anderson et al. (1980) <sup>4</sup>         | 91% Gastric bypass<br>9% Gastroplasty | 11              | 13 yrs     | 85 kg         |                                                                          | <ul style="list-style-type: none"> <li>• 54% required revision due to inadequate wt loss</li> <li>• 1 (9%) wound infection</li> <li>• 1 dumping/diarrhea</li> <li>• 1 death from uncontrolled wt gain</li> </ul> |
| Fonkalsrud and Bray (1981) <sup>74</sup>    | Vagotomy                              | 1               | 17 yrs     | 120 kg        | 29 kg initial wt loss, followed by 20 kg gain                            | 20-kg weight gain                                                                                                                                                                                                |
| Touquet et al. (1983) <sup>185</sup>        | Jejunioileal bypass                   | 1               | 24 yrs     | 181 kg        | 62 kg (1 yr)                                                             | <ul style="list-style-type: none"> <li>• Postoperative wound infection</li> <li>• DVT/pulmonary embolus</li> <li>• 4–5 stools/day</li> </ul>                                                                     |
| Laurent-Jacard et al. (1991) <sup>124</sup> | Biliopancreatic diversion             | 3               | 27.6 yrs   | 84.5 kg       | Significant wt loss 1 <sup>st</sup> year, followed by wt gain (2½–6 yrs) | <ul style="list-style-type: none"> <li>• Diarrhea</li> <li>• Vitamin D, vitamin B<sub>12</sub>, folate, and iron deficiency</li> </ul>                                                                           |



|                                              |                                                        |    |        |            |                                                                             |                                                                                           |
|----------------------------------------------|--------------------------------------------------------|----|--------|------------|-----------------------------------------------------------------------------|-------------------------------------------------------------------------------------------|
| Dousei et al.<br>(1992) <sup>53</sup>        | Vertical banded<br>gastroplasty                        | 1  | 21 yrs | 57.4 kg    | Initial<br>improved<br>DM control                                           | Short-term wt loss<br>followed by break of<br>staple line and wt gain                     |
| Chelala et<br>al. (1997) <sup>43</sup>       | Laparoscopic<br>adjustable gastric<br>band             | 1  | ?      | ?          |                                                                             | Death 45 days<br>postoperatively from GI<br>bleeding                                      |
| Grugni et al.<br>(2000) <sup>88</sup>        | Biliopancreatic<br>diversion                           | 1  | 24 yrs | 80 kg      | Initial wt<br>loss, but wt<br>gain without<br>restriction                   | Diarrhea, severe<br>osteopenia, anemia,<br>hypoproteinemia                                |
| Marinari et al.<br>(2001) <sup>139</sup>     | Biliopancreatic<br>diversion                           | 15 | 21 yrs | 127 kg     | 56%–59% wt<br>loss at 2–3 yrs,<br>then<br>regained<br>10%–20% of<br>wt lost | 2 deaths from unrelated<br>causes<br>(no vitamin levels or bone<br>density data provided) |
| Braghetto et al.<br>(2003) <sup>19</sup>     | 95% gastrectomy<br>with Roux-en-Y,<br>hypocaloric diet | 1  | 15 yrs | BMI = 57.7 | 70 kg weight<br>loss over 1 yr;<br>BMI = 30                                 | No surgical complications<br>reported                                                     |
| Kobayashi<br>et al.<br>(2003) <sup>117</sup> | Roux-en-Y gastric<br>bypass                            | 1  | 30 yrs | 146 kg     | 54-kg<br>weight loss<br>over 18 mos,<br>improved<br>lipid profile           | No complications                                                                          |

children with PWS is not a benign condition since it is associated with severe short stature and an inadequate increase in height velocity.<sup>126,167</sup> Although obesity is thought to be pathogenetic for this condition, there is no evidence that intensive weight control after onset will slow the progress of the adrenarche. Prevention of predisposing factors for premature adrenarche via weight management beginning in very early childhood is the best recommendation at this point. In cases where the process has already started, growth hormone therapy should be considered even if current height is normal in order to optimize final adult height.

### *Insulin Resistance and Type 2 Diabetes Mellitus*

The treatment of insulin resistance and T2DM in PWS should follow current standard-of-care guidelines for these conditions in the non-PWS population. A comprehensive discussion of this topic is beyond the scope of this chapter; the reader is referred to the current literature and healthcare organizations for more detailed protocols (e.g., American Diabetes Association, American Association of Clinical Endocrinologists).

In general, the first-line approach should include diet and exercise, as described above for treatment of obesity and overweight; in milder cases, these therapies may lead to complete resolution of the disorder. Metformin should be considered a first-line pharmacotherapy for insulin resistance, especially if T2DM is present.<sup>42,112</sup> Insulin may be necessary in cases where there is evidence of insulin deficiency (ketoacidosis, unexplained weight loss) but should be avoided in all other cases since it may augment increases in body fat. Sulfonylureas and PPAR-agonists also have a tendency to increase body fat, and the efficacy of these agents in individuals with PWS and T2DM has not been shown. The authors' anecdotal experience suggests that diet, exercise, and metformin are sufficient for treatment of most individuals with PWS and insulin resistance and/or T2DM.

Monitoring of patients with insulin resistance and T2DM should include periodic evaluation of fasting lipid profiles and blood pressure. Fasting insulin levels can be checked periodically, but the clinical utility of this measurement, which can be highly variable, is not defined. Clinically, weight, calculated body mass index, waist circumference, and status of acanthosis nigricans (if present) can be useful.

Individuals treated with metformin should have routine annual monitoring of liver and kidney function tests; an elevated serum creatinine level is a contraindication to therapy. With T2DM, routine home monitoring of fasting and postprandial glucose levels and periodic glycosylated hemoglobin measurements are necessary, with an optimal goal of achieving normal levels for both parameters.

There have been surprisingly few reports of diabetes-related complications in PWS.<sup>8,192</sup> However, individuals with diabetes mellitus should be routinely monitored for evidence of retinopathy, nephropathy, hypertension, and cardiovascular disease, with institution of appropriate therapy as needed as per general standard-of-care practice guidelines.

## Measurement of Body Composition

The measurement and monitoring of body composition has become an essential element in clinical research and management of individuals with PWS. In particular, body composition measurements may be used to diagnose decreased bone mineral density (osteopenia, osteoporosis) and monitor changes in total body fat and nonfat mass.

### Anthropometry

Anthropometry refers to body measurements, such as length or height, weight, circumferences, and skinfold thickness. Although anthropometric techniques (weight-for-height indices, skinfold thickness, waist-to-hip ratio) have been used for many years to indirectly estimate body composition, these techniques are less commonly used for that purpose today. Instead, if detailed body composition analysis is needed, more sophisticated models and techniques are used, as discussed below.

Height growth is an essential feature of human development and should be measured for all children at regular intervals. The measurements should be plotted to the nearest fractional age on charts compiled from the background normal population. Such charts are available for the U.S. pediatric population from the U.S. Centers for Disease Control ([www.cdc.gov](http://www.cdc.gov)). Standards for most other industrialized countries are available. Children under 2 years of age should be measured using recumbent length, which is the basis for these standards. Height velocity charts are also available. Procedures for accurate measurement and calculation of height and velocity are also described on the CDC Web site.

Height growth is basically a measure of long bone (leg, spine) growth, which in turn is dependent on a number of genetic, hormonal, structural, and mechanical factors. Abnormal height growth in children can be the first sign of a systemic abnormality. As mentioned previously, height growth in children with PWS is highly variable but usually abnormally low starting at or before the toddler stage. As shown in several population studies, the average final adult height in PWS is at approximately 2 standard deviations below the mean for the background population.<sup>1,22,36,97,123,149</sup> Scoliosis, if present, may also account for loss of height growth.

Weight is basically a measure of total body mass, regardless of composition. As a stand-alone measurement, it has little intrinsic utility, even if plotted on normative curves. However, the clinical value of a weight measurement is increased when analyzed in conjunction with height, that is, in determination of weight-for-height or body mass index. Assuming that fat and lean mass are present in a predictable proportion (see previous discussion regarding “companionship rule” above), these ratios can provide a measure of body fatness (normative charts available on [www.cdc.gov](http://www.cdc.gov)). However, in conditions where there is an excess proportion of lean mass (e.g., body building) or deficient lean mass/excess fat mass (e.g., PWS), these ratios do not provide an accurate estimation of body fat.

Anthropometric measurements for head circumference, hand and foot length, and other body parts have been published for PWS<sup>28,32,34–36,65,141,196</sup> (see Appendix C). Head circumference measurements are primarily used as an indicator of brain growth in infants and toddlers under 3 years of age. Careful monitoring of head growth is also important for detection of craniosynostosis, premature closure of the cranial sutures resulting in severe neurologic sequelae. One such case in PWS has been published,<sup>66</sup> and the authors are aware of other cases.

Waist circumference and waist to hip circumference ratios have been used to indicate visceral fat and consequent risks for T2DM and cardiovascular disease in non-PWS adults. However, this correlation is likely to be less reliable in PWS since visceral fat may not be increased.

Skinfold thicknesses, measured using calipers at selected body sites, are sometimes used to estimate body fat and non-fat mass. Skinfold thickness is basically a measure of subcutaneous fat. Using assumptions and validated algorithms regarding the proportions of subcutaneous fat to other body compartments, fat and lean mass can be estimated. Although skinfold thickness measurements have been used in several key studies of PWS,<sup>30,54,96</sup> inter-observer variability and lack of validated disease-specific (including PWS) standards and algorithms are major limitations to routine clinical use.<sup>193</sup>

Body Composition Modeling

The first step in determining body composition is to select a model that provides clinically relevant measurements (Figure 6.3). The most extreme form of body composition analysis, elemental or chemical

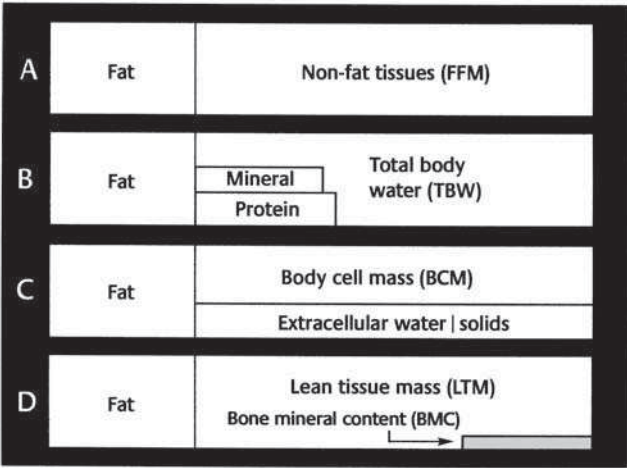


**Figure 6.3.** Multicompartment models of body composition. **A.** Basic 2-compartment model, weight = Fat + FFM (fat-free mass). **B.** Water, protein, and mineral subcompartments of FFM. **C.** Body cell mass and extracellular water and solids subcompartments of FFM. **D.** 3-compartment dual-energy X-ray absorptiometry (DXA) model.

analysis after ashing, is primarily of research interest since it is not feasible in an individual living organism. Elemental analysis can be also performed *in vivo* using isotope counting and neutron activation methods<sup>62</sup>; these measurements currently have limited clinical utility and will not be discussed.

The simplest clinically useful model of body composition, the 2-compartment (2-C) model, divides total body mass or weight (Wt) into fat mass (FM) and fat-free mass (FFM). Body fatness, in turn, can be defined as the FM/Wt ratio, expressed as a percentage. The basic 2-C model requires only one measurement to be made and is the easiest to use when the assessment of body fatness is the primary aim.

More detailed clinical models,<sup>194,195</sup> particularly for considering issues related to nutrition or growth, separate the FFM into components, creating a multicompartment model (Figure 6.3). A useful multicompartment model separates FFM into water and/or protein (muscle) and mineral (bone) subcomponents. Direct assay of FFM components is difficult but has been facilitated by recently developed imaging techniques. These sophisticated techniques, such as dual-energy X-ray absorptiometry (DXA), computed tomography (CT), and magnetic resonance imaging (MRI), allow us to view the components of the living body.<sup>52</sup>

In the following sections of this chapter, the various methods that are available will be described in the context of their application in 2-, 3-, and 4-compartment models of body composition.

### **Methods Based on the 2-Compartment (2-C) Model**

**Underwater Weighing:** For the 2-C model,  $Wt = FM + FFM$ , and  $Vol_{TB} = Vol_{FM} + Vol_{FFM}$  (Total body volume = FM + FFM volumes). An accurate measurement of body weight is relatively easy to achieve, i.e., using a weight scale; the measurement of body volume is more challenging.

The classic technique of measuring body volume, underwater weighing (UWW, or hydrostatic weighing) relies on Archimedes' principle, which states that a body immersed in a fluid is buoyed up by a force equal to the weight of the displaced fluid. The procedure involves measuring body weight while totally submerged underwater, after exhalation of air from the lungs. The body volume is calculated by subtracting the underwater weight from the regularly measured body weight, the weight differential being equal to the weight of displaced water, and dividing the difference by the density of water. This number is adjusted for the measured residual lung volume.

The density of the body ( $\rho_{TB}$ ) is the ratio of body weight (Wt) to body volume ( $Vol_{TB}$ ). The classic UWW relationship between body fatness (%FM) and body density ( $\rho_{TB}$ ) for a 2-compartment model is

$$\%FM = 100 \times \{(k_1/\rho_{TB}) + k_2\}$$

where the constants ( $k_1$ ,  $k_2$ ) are determined by the values selected for  $\rho_{FM}$  and  $\rho_{FFM}$  (densities of the fat and fat-free mass).<sup>24,173</sup> The density of fat can be assumed to be constant (0.9004 g/cc), whereas the density of FFM is not constant, changes with growth,<sup>134</sup> and is altered by diseases and medications. Since body water is the major contributor to the

mass and volume of the FFM, changes in the relative water content (hydration) will have significant effects on  $\rho_{\text{FFM}}$ . Other components of the FFM can also change, but these have a secondary impact compared with hydration.

For short-term longitudinal studies in healthy subjects, using age- and gender-adjusted constants, the 2-C model is adequate for the assessment of changes in body fatness. However, it does not provide information about components of the FFM.

*Air-Displacement Plethysmography:* There can be several reasons why the underwater weighing technique cannot be used, e. g., lack of necessary equipment, fear of water, difficulty breathing underwater, too buoyant to be easily submerged. An alternative technique called air-displacement plethysmography (ADP) can also be used to measure body volume. The advantage of ADP is that the problems related to water are eliminated, although the subject still needs to wear a tight-fitting bathing suit and cap to cover scalp hair. The objective is to determine the volume of air that is displaced by the subject's body.<sup>68,134</sup> At present, there are only two commercial ADP instruments available (BODPOD for adults and PEAPOD for infants, Life Measurements Inc., Concord, Calif.).

The ADP technique is based on Boyle's Law for gases: pressure multiplied by volume is constant if temperature does not change. Poisson's Law for gases is also used in order to adjust for the subject's breathing (heated moist air coming from the lungs) and for the isothermal effects of air in contact with the subject's skin and body hair.

For the BODPOD measurement, the subject sits on a bench in a small test chamber that is about the size of a telephone booth. This chamber is connected via a diaphragm to a reference chamber behind the bench. The door (which has a large window) is closed, the diaphragm is oscillated at a low frequency, and the pressure difference between the two chambers is measured. The BODPOD instrument also has a built-in spirometer system that can be used to measure the subject's residual lung volume. It should be noted that without preliminary training, the spirometer procedure can be difficult for some subjects to perform correctly.

ADP estimates of body volume are highly correlated with those for UWW, and the two results are virtually interchangeable for healthy adults.<sup>68</sup> Additional studies with children may be needed, especially where body composition may be abnormal. However, it is reasonable to expect that the ADP technology may replace the underwater weighing technique for 2-C analysis in adult and pediatric populations.

*Total Body Water and Potassium:* Two alternate methods can be used in a 2-C model to estimate body fatness by measuring body water and cellular components of the FFM. The body composition parameters that are measured for these methods are total body water (TBW) or total body potassium (TBK), respectively.<sup>60,62</sup>

For these two assays, the simple 2-C equations for body fatness are as follows:



$$\%FM_{TBW} = 100 \times (Wt - TBW/k_3)$$

$$\%FM_{TBK} = 100 \times (Wt - TBK/k_4)$$

where the values for  $k_3$  and  $k_4$  are assumed to be relatively constant at a given age for a healthy subject. However, during infancy and childhood, the relative hydration and potassium content of the total FFM are not constant, and they may also be altered by disease and/or medications.<sup>60</sup> That is, the same limitations that were possible for the 2-C UWW or ADP models are also present for the 2-C TBW and TBK models. This is an inherent limitation of the 2-C model and not the methods. An advantage of the TBW and TBK assays, compared with UWW or ADP, is that these assays provide useful information on their own about the composition of FFM.

For the TBW assay, the subject drinks a small amount of isotope-labeled (non-radioactive) water. Several hours later, a body fluid sample (blood, urine, or saliva) is collected and stored for later analysis using isotope-ratio mass spectroscopy (MS) or Fourier-transformed infrared spectroscopy (FT-IRS). Since the amount of the tracer given to the subject is known, and its concentration in the water part of the fluid sample is measured, the total volume of the dilution space can be easily calculated.<sup>168</sup> The value for the conversion constant ( $k_3$ ) that is used most often is 0.732 for older children and adults, gradually increasing to 0.83 for infants. That is, FFM contains, on average, about 73.2% water for healthy children and adolescents. This percentage, however, may be altered with diseases, such as severe malnutrition or edema, and by some drugs. A clear advantage of the TBW technique is that bulky instrumentation is not needed at the times of isotope administration and sample collection, thus making it a suitable choice for field studies. The MS or FT-IRS analysis could be performed immediately, but the usual practice is to collect multiple samples for batched analysis, thus the TBW results are often delayed until some time after the actual procedure.

The results of the TBK assay, on the other hand, can be obtained immediately. This assay takes advantage of a natural signal that is being constantly emitted from the potassium in the human body. A small fraction of natural potassium is radioactive ( $^{40}\text{K}$ ), emitting characteristic gamma rays (1.46 MeV) at the rate of about 200 gammas per minute per gram of potassium. This signal can be detected external to the body using a whole-body counter,<sup>63</sup> usually a whole-room shielded counting chamber. Based on numerous studies over the past 40 years, the values for the conversion constant ( $k_4$ ) are estimated at 59 to 61 mEq/kg for adult females and 62 to 64 mEq/kg for adult males. For infants, the ratio is reduced to ~43 mEq/kg because of increased hydration.<sup>60,61</sup> A major limitation with this assay is that the measurement instruments are not portable, and the number of available instruments and facilities is very limited. However, it is well recognized that the TBK assay is the best choice for monitoring body cell mass (BCM), the active metabolizing tissues of the FFM.<sup>60</sup> In many diseases, knowledge of the patient's BCM status has a higher priority than knowledge of body fatness.

*Bioelectrical Impedance:* The bioelectrical techniques for assaying body composition were developed as alternatives to the isotope dilution assay of total body water. The attractiveness of this technology is that the instruments are small in size, relatively inexpensive, don't require extensive operator training, and the results are immediately available. The principle of the bioelectrical impedance technique is that the body has general electrical properties, which primarily reflect the volume of the FFM and its electrolyte content.<sup>90</sup> Three approaches have been developed for human use: (1) single frequency (50 kHz) bioelectrical impedance analysis (BIA), (2) multifrequency (5–1000 kHz) bioelectrical impedance spectroscopy (BIS), and (3) total body electrical conductivity (TOBEC).

For the BIA and BIS procedures, pairs of electrodes are attached at the hand and foot. A weak electrical current is passed between the electrodes, and resistance (R) and reactance (Xc) are measured. The BIA assay uses a single frequency (50 kHz), while the BIS technique varies the frequency (5–1000 kHz). The basic BIA and BIS theory results in the assumption that the  $Ht^2/R$  ratio is directly proportional to TBW or FFM.<sup>10</sup> Some BIA instruments have been designed to measure only the upper body (electrodes placed on the hands) or lower body (subject stands in the electrodes), while other investigators have chosen to perform segmental BIA measurements (placing multiple electrodes at many sites on the body).

There are at least 30 single-frequency BIA devices commercially available. Unfortunately, there are almost an equal number of algorithms to choose from for the calculation of TBW, FFM, or %FM. Furthermore, some investigators have suggested that disease-specific calibrations of BIA should be used.<sup>191</sup> Although this approach may, at first, appear attractive, this type of "work around" simply avoids the more difficult issues related to the limited accuracy of the basic BIA theory and algorithms.

For the total body electrical conductivity (TOBEC) assay, no electrodes are placed on the body. Instead, the body passes through a large diameter electrical coil. The free charge particles in the body will attempt to align with the external magnetic field within the bore of the coil, causing a small measured perturbation in the coil current. The procedure takes only a few minutes to perform, and can be repeated as frequently as needed without risk to the subject.

Similar to the BIA and BIS assays, the TOBEC technique is a secondary assay, which means that the measured value (called the TOBEC number) must be calibrated with a more direct assay of FFM or TBW. A limitation with the TOBEC instrument is that it is very large compared with the BIA and BIS devices; hence it is not portable, and its initial cost is substantially higher. Thus, the number of TOBEC instruments worldwide is extremely limited, as with those based on the TBK technique.

### ***Methods Based on the 3-Compartment (3-C) Model***

*Body Density + TBW:* As pointed out for the 2-C density models (UWW and ADP), the major limitation was the assumption that TBW was a

fixed percentage of the total FFM. This constraint can be overcome by using a 3-compartment (3-C) density model where the measurement of TBW is included. In this case, the %FM equation becomes:

$$\%FM = 100 \times \{(2.118rTB) - 0.78 TBW/Wt - 1.354\}$$

where the density of body fat and solids are 0.9004 g/cc and 1.565 g/cc, respectively. The advantage of this model is that the hydration state of the FFM can be variable, without introducing additional error in the estimate for body fatness. The disadvantage is that two assays (UWW or ADP and TBW) are needed, which increases the complexity and decreases feasibility of the procedure.

*Dual-Energy X-ray Absorptiometry:* Absorptiometric techniques were developed in the 1960s to examine bone because of the concerns that astronauts would experience significant bone loss during space flight. Over the last 40 years, significant advances have been made with this technology, evolving into the current technique, called dual-energy X-ray absorptiometry (DXA).<sup>62</sup> DXA assays of the hip and spine have become the clinical standards for the assessment of bone mineral density, used to screen for the increased risk of bone fractures, especially in postmenopausal women. In addition, a whole body DXA can be obtained in approximately 3 minutes with a very low total radiation dose (<10 μSv).

During a DXA procedure, the subject lies supine on the exam table, clothed but with removal of metal objects. An X-ray scanning arm passes over the selected body parts or the whole body. The X-rays are attenuated during passage through body tissues. The net signal is detected, converted into pixels, and analyzed using algorithms. For diagnosis and monitoring of osteoporosis, the scan is usually limited to the hip and/or lumbar vertebral spine, which are sites that are prone to osteoporotic fragility fractures. For more complete body composition analysis, a whole body scan is obtained.

In order for DXA to provide a quantitative measure of bone, the physics requires that the density of the overlying soft tissue must be known. This is accomplished by analyzing the nonbone pixels in the image next to the bone-containing pixels for their relative fat-to-lean content. Thus, a whole-body DXA scan can be used to produce a quasi-3-compartment (3-C) model: bone mineral content (BMC), fat mass (FM), and nonbone lean tissue mass (LTM). The sum of the bone-containing pixels provides a measurement called the bone area (BA), and areal bone mineral density (BMD) is defined as BMC/BA. It is to be noted that the DXA-derived BMD (g/cm<sup>2</sup>) value is not true bone density (g/cm<sup>3</sup>) but a projection of the total body mass onto a 2-dimensional or plainer image of the body.

A clear advantage of whole-body DXA is that the body scan image is divided into 10 general regions (head, arms, legs, trunk, pelvic, spine, etc.) with BMC, BMD, fat, and LTM calculated for each region. Thus, not only can the body FM be examined but also its regional distribution. Although this information is useful, it does not, for example, distinguish between subcutaneous fat and visceral fat stores in the body.

### *Methods Based on Body Imaging Techniques*

To obtain precise body composition information, anatomical imaging techniques, such as computed tomography (CT) and magnetic resonance imaging (MRI), are used. The CT technique uses collimated beams of X-rays that are passed through the body, and an array of detectors is positioned on the opposite side of the body to detect the transmitted signal.<sup>62</sup> The X-ray source and detector assembly are rotated as a single unit around the body, and the data are collected and reconstructed to generate a cross-sectional image or “slice” of the body for each rotation. The physics of the CT procedure makes it a quantitative assay, i.e., the relative density (g/cc) of each pixel in the cross-sectional image can be obtained. Thus, anatomical regions such as the subcutaneous adipose tissue (SAT) layer, muscle, skin, internal organs, bone, and visceral fat deposits (VAT) can be identified. A disadvantage with routine CT imaging is that the radiation exposure is higher than that needed for a DXA scan, and whole body or extensive regional scans are not feasible.<sup>23</sup> The image requirements for a clinical CT scan can be relaxed when it is used for body composition analysis, such as for determination of VAT and SAT, which reduces the dose significantly.<sup>177</sup>

Magnetic resonance imaging (MRI) also provides internal images of the body, which tend to be superior in anatomical quality to those obtained using CT. One can easily identify the subcutaneous and visceral fat areas, for example, in an abdominal MRI image. However, the quantitative quality of the MRI image is much less than that obtained with the CT scan, and a whole body MRI can take up to 10 times longer to perform than a DXA. On the other hand, the MRI technique has several advantages, including the ability to distinguish VAT and SAT, and the system can be tuned to respond specifically to lipids contained within the lean tissues.<sup>137,166</sup> This may help to better understand the association of excess adiposity with some chronic diseases, such as T2DM.<sup>114</sup>

### **Methods Selection**

The pathogenesis of PWS involves alterations in body composition that are atypical for human physiology and pathophysiology. In particular, there is an inherent increase in fat mass that is disproportionate to lean mass regardless of weight. The distribution of this fat mass could be relevant to defining cardiovascular risk. Lean mass is extremely deficient, as reflected in the hypotonia and decreased spontaneous activity. Finally, bone mineral density tends to be low, particularly in older individuals with PWS, increasing the risks for osteoporosis and fragility fractures. Given these considerations, body composition monitoring is an important element of clinical care for individuals with PWS. However, the selection of methods can be confusing.

As discussed above, there are a number of techniques that can be used to examine human body composition,<sup>62</sup> each with its own sets of advantages and disadvantages. Two-compartment (fat, nonfat) and 3-compartment (fat, bone, nonbone lean) models have been the most

popular and clinically feasible. Higher-level models may provide a more complete picture of body composition, but multiple assays are required, some of which are not routinely found in most institutions.

In terms of 2-compartment models, the BIA technique has become widely available partly because it is relatively easy to perform, requires minimum investment, and is portable (for field studies or bedside use). Unfortunately, the body composition results are often not much better than those obtained using anthropometric measurements, such as body mass index calculations or skinfold measurements.

For more accurate 2-compartment modeling, air displacement plethysmography (i.e., using the BODPOD instrument) offers an attractive alternative to the more difficult underwater weighing technique.<sup>68</sup> However, the feasibility of this procedure in PWS has not been tested. In addition, although the methods for 2-compartment modeling are designed to measure fat-free mass (with fat mass calculated as the residual), they have the disadvantage of not providing additional information regarding the nonfat component (i.e., bone and nonbone lean mass).

Table 6.3 summarizes key considerations for body composition measurement methods, classified by the measured component. Costs are based on 2004 U.S. estimates. Precision and accuracy of each method are listed, as well as the minimal detectable change.

For practical purposes, the DXA procedure has become the reference method for the clinical assessment of bone mineral. This clinical acceptance of DXA, and its accessibility at many institutions, is also driving the use of this technique as a reference for the measurement of body fatness and lean mass. For patients with PWS, the DXA procedure has the additional advantages of rapidity, minimal patient cooperation requirements, and provision of measurements for all three clinically relevant body compartments. The 1% to 3% analytical precision of the DXA method allows detection of relatively small longitudinal changes in bone, fat, and nonbone lean tissues. However, there are significant differences in the calculation of %FM by DXA versus more sophisticated techniques; therefore, further improvements in DXA may be needed before a consensus can be reached<sup>186</sup> regarding the utility of DXA in estimating FM and nonbone lean mass. In addition, DXA methodologies differ according to manufacturers; results are not directly interchangeable; and pediatric, age-related, and ethnic normal ranges have not been widely accepted.<sup>9,62,122,200</sup> A minor disadvantage of DXA is that an exposure to X-rays is required; however, the dose is very small ( $>10\mu\text{Sv}$ ) and carries minimal risk. From a practical standpoint, the DXA platform has body weight limitations; scans cannot be performed on individuals over 300 pounds on some commonly used DXA machines.

Single-slice abdominal CT and MRI methods are excellent choices when information about the distribution of body fat in the abdominal region is important. This information could have relevance to defining cardiovascular risk; however, these methods have not yet been validated for monitoring of individual patients, PWS or otherwise. In addition, these methods do not provide information about whole body tissue status.

Table 6.3. Comparison of Body Composition Methodologies

| Measured Compartment | Method                          | Instrument Cost (US\$) | Procedure Charge (US\$) | Precision % | Accuracy % | MDC <sup>i</sup> Amt. (%)               |
|----------------------|---------------------------------|------------------------|-------------------------|-------------|------------|-----------------------------------------|
| Total Body Water     | Deuterium dilution <sup>a</sup> | 25–70 K                | 50–100                  | 1–2         | 2–3        | 2 L (5)                                 |
|                      | BIA/BIS <sup>b</sup>            | 3–7 K                  | 30                      | 2–4         | 3–7        | 4 L (10)                                |
|                      | QMR <sup>c</sup>                | 100 K                  | —                       | 1           | —          | 1 L (3)                                 |
| Fat-Free Mass        | UWW <sup>d</sup>                | 25–35 K                | 45                      | 1–2         | 2–3        | 2 kg (4)                                |
|                      | ADP <sup>e</sup>                | 30–80 K                | 45                      | 1–2         | 2–3        | 2 kg (4)                                |
|                      | BIA/BIS                         | 3–7 K                  | 30                      | 2–4         | 2–8        | 4 kg (7)                                |
|                      | DXA <sup>f</sup>                | 125 K                  | 150                     | 2           | 1–2        | 1 kg (2)                                |
| Fat Mass             | DXA                             | 125 K                  | 150                     | 2–3         | 3–5        | 2 kg (11)                               |
|                      | CT <sup>g</sup>                 | 800 K                  | 350                     | 3–4         | 3–4        | — (10)                                  |
|                      | MRI <sup>h</sup>                | 1500 K                 | 600                     | 3–4         | 3–4        | — (10)                                  |
| Bone Mineral Density | DXA                             | 125 K                  | 150                     | 1           | 2–3        | 0.04 g/cm <sup>2</sup> (4) <sup>j</sup> |
|                      | CT                              | 800 K                  | 175                     | 1           | 1          | 1.2 mg/cc (1) <sup>k</sup>              |

<sup>a</sup> Requires baseline body fluid sample, such as plasma, and 2–4 hours post-dose sample. Can be assayed using infrared spectroscopy or mass spec.; results are not “immediate,” 2nd assay must be delayed 15–30 days to allow for initial dose to clear. Use of <sup>18</sup>O instead of deuterium results in 5–10-fold increase in assay cost.

<sup>b</sup> Single (BIA) and multifrequency (BIS) bioelectrical impedance analysis. At least 30 commercial instruments, with equal number of prediction equations. Can be repeated as needed.

<sup>c</sup> Quantitative magnetic resonance has only been used with small animals, but has been shown to be more accurate than dilution method and can be repeated as needed without harm. Magnetic field strength is about 1/200 of routine MRI instruments.

<sup>d</sup> Underwater weighing, requires subject to be totally submerged in water while air is exhaled from lungs. Classic method in use for more than 50 years, limited use for infants and older adults.

<sup>e</sup> Air-displacement plethysmography replaces underwater weighing method. Easily tolerated by subjects, can be repeated as frequently as needed, and both adult and infant-sized instruments are available.

<sup>f</sup> Dual-energy X-ray absorptiometry. Often considered as “gold standard” for *in vivo* bone mineral measurement. Gives regional information about body fat distribution.

<sup>g</sup> Computed tomography gives information about internal distribution of fat. Most frequently used to assay subcutaneous and visceral fat components of abdominal fat. Scan times in seconds, but frequency of repeat scans is limited by the radiation dose.

<sup>h</sup> Magnetic resonance imaging gives information and image of internal distribution of fat. Can be repeated as needed, but requires substantially longer time than CT.

<sup>i</sup> Minimum detectable change (MDC) for an individual. Value in parenthesis is the change expressed as a percent based on body composition of a 79-kg male with 25% fat. For CT and MRI, a 10% change in either fat subcompartment should be detectable.

<sup>j</sup> Values are for areal bone mineral density; similar values for total body, spine, or hip DXA.

<sup>k</sup> True density of bone, usually performed only for the spine.

In summary, with the various techniques that are available today, it is possible to obtain an accurate *in vivo* assay of the human body and to monitor the changes with growth or treatment of diseases. DXA is currently the most useful procedure for assessment of body composition in individuals with PWS; however care should be exercised in the proper interpretation of results.



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# Growth Hormone and Prader-Willi Syndrome

Aaron L. Carrel, Phillip D.K. Lee, and Harriette R. Mogul

In the previous edition of this textbook, various lines of evidence for the occurrence of a deficiency in the growth hormone (GH) axis were reviewed as one of several sections in a chapter entitled “Endocrine and Metabolic Aspects of Prader-Willi Syndrome.”<sup>76</sup> At that time, it was suggested that GH therapy may have beneficial effects on growth and body composition in individuals with PWS. Over the succeeding decade, a number of scientific investigations have provided definitive evidence in support of these suggestions.<sup>16,37,72,73</sup> In 2000, biosynthetic GH became the first and, to date, only medication to receive regulatory approval for treatment of children with PWS. In addition, it appears that GH may also have potential utility in adults with PWS.<sup>61,86</sup> This chapter presents a comprehensive review of relevant physiology and pathophysiology of the GH system and GH treatment efficacy and safety in PWS.

## GH/IGF Axis Pathophysiology

Short stature is one of the cardinal features of PWS and was included in the initial description<sup>98</sup> of the condition in 1956. Numerous studies have shown that growth is usually compromised during childhood and that the average final adult height is approximately 2 standard deviations below the mean for the normal population<sup>1,15,19,34,48,57,59,60,70,89,91,124</sup> (see Appendix C). In individual cases, final adult height has been noted to be related to midparental height—i.e., PWS individuals with taller parents will be relatively taller than other PWS individuals<sup>18,97</sup>; however, final height is virtually always significantly lower than the actual midparental height in the usual case of PWS. Although a proportion of children with PWS will have accelerated growth and normal stature during childhood, often in association with premature adrenarche, final adult height in these cases may be further compromised by the accelerated bone maturation (see previous chapter). Thus, PWS is one of only a few conditions in which obesity is associated with short stature and is clearly distinguished from exogenous obesity, in which

childhood linear growth is accelerated and final height is normal or increased.<sup>46</sup>

Early investigators suspected that growth hormone (GH) deficiency might be involved in the pathogenesis of the short stature, and several studies have shown deficient serum GH levels in response to standard stimulation tests in children<sup>4,15,20,21,29,48,78,91,94,114</sup> and adults<sup>62,95</sup> with PWS. However, these results may not be entirely convincing since GH levels are low in non-PWS obesity that is not associated with short stature.<sup>67</sup>

GH is synthesized in the anterior pituitary gland and released into the bloodstream. GH itself is thought to have minimal, if any, effect on somatic growth. Instead, GH stimulates synthesis of other growth factors in liver and other tissues. These growth factors then act to stimulate growth of body tissues, including bone and muscle.

One of the primary growth factors that mediate the GH effects is insulin-like growth factor-I (IGF-I). In true GH deficiency, IGF-I levels are very low, and this is associated with decreased linear growth. On the other hand, in common exogenous obesity, GH levels are low but IGF levels are normal or elevated,<sup>67</sup> and this is associated with normal linear growth. IGF-I is carried in the bloodstream by several specific binding proteins, including IGFBP-3. Therefore, measurement of either serum IGF or serum IGFBP-3 levels provides an indirect measure of GH secretion and a direct measure of the GH/IGF axis.

Reliable laboratory assays were developed for IGF-I in the mid-1970s and for IGFBP-3 in the mid-1980s. Since then, IGF-I and IGFBP-3 levels have been reported to be abnormally low in both children and adults with PWS<sup>3,28,29,45,56,62,64,75,78,81,99</sup>. The combination of low GH and low IGF-I argues for the existence of a true GH/IGF axis deficiency in PWS.<sup>38,76</sup>

GH/IGF axis deficiency is also suggested by the body composition characteristics in PWS. As discussed in the preceding chapter, both fat and lean mass compartments are increased in common exogenous obesity. However, in PWS, fat mass is preferentially increased,<sup>14,74</sup> a condition that is also found in other forms of GH deficiency.<sup>27</sup>

Although the composite data strongly support the existence of a GH/IGF axis deficiency, a small but significant proportion of individuals with PWS will have normal GH responses on standard testing. In many of these cases, the IGF-I levels are low and growth and body composition are characteristic for PWS and GH deficiency. This paradoxical situation may be explained by the physiology of the GH/IGF system and limitations of GH testing.

GH (somatotropin) is secreted by specialized cells (somatotropes) in the anterior pituitary gland in an episodic manner; bursts of GH are released into the bloodstream in an intermittent and somewhat unpredictable pattern, with each burst having a relatively short half-life in serum. The pattern of these bursts is regulated by a complex system, involving inhibition of GH release by intermittent secretion of somatostatin (inhibitory) and GH-releasing factor (stimulatory) from the arcuate nucleus of the hypothalamus, coupled with negative feedback

signals from the periphery to the CNS.<sup>47</sup> Larger bursts of GH release are observed during fasting, exercise, sleep, and during puberty. Between these bursts, GH levels are normally low. The total daily secretion, or total area-under-the-curve, for GH is presumably proportionate to the levels of IGF-I.

Because of this episodic secretion, random GH levels have little utility in the assessment of GH adequacy since these levels are likely to be low. Therefore, various testing protocols are used to predictably stimulate GH secretion, using either physiologic (fasting, monitored exercise) and/or pharmacologic (insulin-induced hypoglycemia, clonidine, arginine, ornithine, L-DOPA, glucagons) stimuli followed by repeated, timed blood sampling.

Although provocative GH testing has been a widely accepted diagnostic procedure for many decades, there is considerable controversy regarding reliability and clinical usefulness.<sup>51</sup> A large proportion of individuals will fail to achieve a normal GH peak on one test but not another, resulting in a requirement for two or more tests. In addition, individuals who fail testing in childhood may have a normal response when tested at a later time. Furthermore, there is lack of agreement on the definition of a “normal” response level, with published criteria ranging from a peak GH level of 3–15 ng/mL, and this is further complicated by considerable variability between assay methods.

Finally, there are questions regarding the physiologic relevance of GH secretion. GH is undoubtedly the major factor that stimulates secretion of growth-promoting factors such as IGF-I. However, other factors are also involved. For instance, in some individuals who have GH deficiency due to craniopharyngioma, IGF-I levels and linear growth are normal. This latter situation is thought to be due to hyperphagia and obesity, with high insulin levels stimulating IGF-I synthesis. In addition, children with short stature and growth failure may have low IGF-I levels despite normal or high GH levels; the extreme example of this situation involves defects in the GH receptor. Therefore, although very low GH levels are indicative of pituitary dysfunction, neither high nor low levels are necessarily predictive of IGF-I levels or linear growth patterns.

Returning to PWS, it is evident that the majority of individuals have a deficiency in IGF-I and characteristics of GH deficiency, although many patients will have apparently normal stimulated GH levels. The specific reasons for this discordance in PWS are not entirely known. However, several points should be considered:

1. There is no evidence for GH resistance as might be observed, for instance, with GH receptor defects. GH levels are not high and a therapeutic response is seen with usual GH replacement therapy.
2. There is no evidence for an IGF-I synthetic defect in response to GH; IGF-I levels increase during GH replacement therapy (see below).
3. The low GH levels could be related to obesity, as is seen with exogenous obesity. However, in this latter situation, inhibition of GH

secretion is thought to be due to excess free fatty acids<sup>85</sup>; free fatty acid levels are not elevated in PWS.<sup>12,85,113</sup>

4. GH deficiency in PWS has been attributed to intrinsic hypothalamic dysfunction; however, as discussed in previous sections, there are no definitive data in support of this hypothesis, nor for the alternate hypothesis of a defect in peripheral signaling.<sup>77</sup>

5. The fact that stimulated GH levels are normal in a significant proportion of individuals with PWS implies that there is no intrinsic defect in pituitary GH synthesis associated with the syndrome. However, GH testing is acknowledged to be nonphysiologic;<sup>51</sup> therefore, the possibility of a defect in the daily regulation of pituitary GH secretion cannot be completely excluded. Low levels of IGF-I could be due to low total daily secretion of GH despite normal stimulated levels. This latter hypothesis is supported by the positive response to GH therapy in PWS.

6. The lack of normal IGF-I levels despite hyperphagia and obesity, as might be expected from the experience with craniopharyngioma patients,<sup>96</sup> could in part be due to the lack of insulin resistance and hyperinsulinemia in PWS (see preceding chapter).

In summary, short stature and body composition abnormalities in PWS are consistent with a defect in the GH/IGF axis.<sup>38,76</sup> Although the exact mechanisms have not been delineated, an insufficient production of IGF-I is evident in most cases. The composite data indicate that a complete defect in pituitary GH synthesis may not be involved, although stimulated GH levels are low in a considerable proportion of cases.

As a final comment to this discussion, although GH therapy was historically specified for use in GH deficiency, increased availability of biosynthetic GH has led to its use in a number of conditions that do not necessarily involve GH deficiency. In addition to PWS, current regulatory labeling for GH use in the U.S. and Europe includes childhood growth failure associated with several conditions in which GH and/or IGF-I levels are typically normal (chronic renal failure, Turner syndrome, small for gestational age, idiopathic short stature) and adult HIV-associated wasting. Therefore, while the evidence for GH/IGF axis deficiency provided impetus for investigations of GH therapy in PWS, current therapeutic recommendations are guided primarily by overall treatment efficacy.

## GH Therapy

GH was first identified in the 1920s, with purification of primate GH achieved in the 1950s.<sup>50</sup> Therapeutic use in a child with GH deficiency was first reported in the late 1950s. Until 1985, GH was available only as a purified preparation from animal sources and human cadaver donors, and non-primate GH was found to be relatively ineffective in humans. A U.S. national program had been initiated in 1963 (and shortly thereafter in other countries) to collect donated human cadaver pituitary glands and purify GH for therapeutic use. This very limited,

sporadic supply was distributed gratis to GH-deficient children through an application and approval process. In 1978, commercial supplies of cadaver-derived human GH became available.

In 1985, a case of Creutzfeldt-Jakob disease, a fatal neurodegenerative disorder, was reported in a patient who had received cadaver-derived human GH.<sup>58</sup> Other cases were identified worldwide and were suspected to be due to transmission of an infectious agent in the cadaver-derived GH preparations. Cadaver-derived GH was removed from clinical use and replaced by biosynthetic GH, manufactured through recombinant DNA technology. No cases of Creutzfeldt-Jakob disease have been reported in patients treated with synthetic GH. In addition, the cause of this disease was recently confirmed to be an unusual infectious agent, called a prion, which was probably transmitted via impurities in the cadaver-derived GH preparations.<sup>121</sup>

At the time of its precipitous release into the marketplace in 1985, synthetic GH had not yet gone through complete safety and efficacy trials. Therefore, a system of postmarketing surveillance was established by agreement between the GH manufacturers and the U.S. Food and Drug Administration. In 1987, Genentech Inc. established the National Cooperative Growth Study (NCGS) in the U.S.<sup>123</sup> and Kabi Pharmaceuticals (now Pfizer) established the Kabi International Growth Database (KIGS).<sup>100</sup> Over the subsequent years, additional post-marketing studies have been initiated for GH and other pharmaceuticals in the U.S. ([www.fda.gov/cder/pmc](http://www.fda.gov/cder/pmc)) and throughout the industrialized world, providing information regarding safety and efficacy of prescription medications.

In addition, the increased supply of GH has opened the doors for treating conditions other than childhood GH deficiency. Other U.S. FDA-approved indications and the year of approval include: childhood Turner syndrome (1996), childhood growth failure due to chronic renal failure (1997), HIV-associated wasting in adults (1998), adult GH deficiency (1998), childhood PWS with growth failure (2000), childhood growth failure in children who were small for gestational age at birth (2001), childhood severe idiopathic short stature with abnormally low predicted adult height (2003), and in patients with short bowel syndrome who require nutritional support (2003). It should be noted that the European regulatory labeling for GH in PWS is “for improvement of growth and body composition in children,” while the U.S. labeling specifies “long-term treatment of pediatric patients who have growth failure due to Prader-Willi syndrome” without mention of the important beneficial effects of GH (Genotropin and Genotroponorm package inserts, Pfizer). Labeling in other countries tends to follow the European indications.

The first preparations of synthetic GH were provided as lyophilized powder, which was then reconstituted with liquid diluent by the user and injected using an insulin syringe. This type of preparation is still available. However, pen injection devices, using GH cartridges and disposable needles, are perhaps the most popular modality in use

today. Disposable single- and multi-dose and nondisposable needle-free air injection devices are also available. All commercial GH preparations in use today are biochemically identical to natural human GH and are highly purified.

## Effects of GH Treatment in Prader-Willi Syndrome

### Linear and Other Skeletal Growth

Initial studies of the effect of GH treatment of children with PWS focused on growth rate acceleration and improvement in stature as primary therapeutic goals. Early reports showing that GH treatment increases growth rate in PWS children did not include control subjects and were relatively short-term.<sup>4,32,56,74,75</sup>

Recent longer-term studies (2–5 years) have provided additional evidence supporting a significant and sustained growth response to daily GH administration.<sup>3,26</sup> Favorable effects on growth were noted in a Swedish study of 18 children with PWS treated with GH for 5 years.<sup>83</sup> A Swiss study of 23 PWS children treated with GH for a median of 3.5 years showed an increase in mean height standard deviation score (SDS) of 1.8, with adult height predictions approaching midparental target height.<sup>41</sup>

In a treatment/no treatment control study, height velocity increased from –1.9 to +6.0 SDS during the first year of GH administration (0.1 IU/kg/day) in 15 children with PWS, compared with a decrease from –0.1 to –1.4 SDS in the no-treatment group (n = 12). For the treatment group, this corresponded to a mean growth rate of approximately 12 cm/year, which is greater than that observed for virtually all other conditions treated with GH.<sup>81</sup>

Small hands and feet (acromicria) were also positively affected by GH therapy, tending toward normalization in children with PWS.<sup>37,41,88</sup> Arm span and sitting height showed similar trends.<sup>37</sup>

### Body Composition and Metabolism

GH treatment of GH-deficient children without PWS not only restores linear growth, but also promotes growth of lean body mass, decreases fat mass by increasing fat oxidation and total body energy expenditure, increases bone mineral density following an initial period of increased bone resorption, and improves cardiovascular risk factors.<sup>68,122</sup> Children with PWS respond to GH therapy with similar improvements in body composition and metabolism, and these effects are arguably more valuable than change in growth velocity.

Increased lean body mass and bone density have been reported in several uncontrolled studies of GH therapy in children with PWS.<sup>31,40,74,80</sup> Favorable effects to reduce absolute or percent body fat have also been reported, although these effects are less consistent than for lean body mass and bone density,<sup>3,40,74</sup> as may be expected due to the overall variability in calorie intake, energy output, and body weight in the general population.



In a recent trial in children with PWS, dramatic improvements in lean body mass, bone density, and linear growth were demonstrated in the GH-treated group ( $1.0\text{mg}/\text{m}^2/\text{day}$ ) as compared with a nontreated group over the first year.<sup>23</sup> Fat utilization was also increased, while percent body fat stabilized or decreased in most subjects. Over subsequent years of the study, in which the nontreated group was crossed over into treatment, progressive increases in lean body mass and linear growth and continued beneficial effects on body fat were noted.<sup>11,22,23,24,88</sup>

In the same study, a dose response was noted during the dose-ranging study at 24 to 48 months.<sup>26</sup> During this study period, continued progressive increases in lean body mass and height improvement and stabilization of percent fat occurred with administration of either  $1.0\text{mg}/\text{m}^2/\text{day}$  or  $1.5\text{mg}/\text{m}^2/\text{day}$  of GH, but not with a lower dose of  $0.3\text{mg}/\text{m}^2/\text{day}$ . Prior improvements in bone mineral density were sustained regardless of dose. The GH treatment responses in children with PWS are greatest during the first 12 months, as is typically observed for other types of childhood GH treatment. The rates of positive changes in lean body mass and bone mineral density slowed but did not regress during more prolonged GH therapy at doses  $\geq 1.0\text{mg}/\text{m}^2/\text{day}$ , and continued to be higher than expected compared with reference data for healthy children without PWS.

Given their reduced lean body mass, children with PWS would be expected to demonstrate markedly reduced resting energy expenditure (REE). Prior to GH treatment, children with PWS showed reduced REE compared with predicted values for non-PWS children matched for surface area ( $22.4 \pm 4.4\text{kcal}/\text{m}^2/\text{hour}$  versus  $43.6 \pm 3.2\text{kcal}/\text{m}^2/\text{hour}$ ;  $p < 0.0001$ ).<sup>26</sup> GH therapy increased REE in children with PWS in parallel with changes in lean body mass, with a similar dose-dependence; i.e., effects were noted at both  $1.0\text{mg}/\text{m}^2/\text{day}$  and  $1.5\text{mg}/\text{m}^2/\text{day}$  of GH but not with a lower dose of  $0.3\text{mg}/\text{m}^2/\text{day}$ .

GH deficiency is associated with lipogenesis and fat storage predominating over the accretion of lean mass, even in the absence of overt obesity. Preference for fat utilization as an energy source is reflected in a reduction of respiratory quotient (RQ). The RQ normally ranges from 0.7 (strong predominance of fatty acid oxidation) to 1.0 (exclusive oxidation of carbohydrate) to  $>1.0$  (indicating lipogenesis from carbohydrate). GH treatment in PWS children was associated with a decrease in RQ values, indicating increased utilization of fat for energy.<sup>26</sup> Thus, compared with non-GH-treated PWS controls, GH-treated PWS patients demonstrated a shift in energy derived from oxidation of fat, coincident with reductions in fat mass.

### Muscle and Respiratory Function

As reviewed in a previous chapter, decreased muscle mass, hypotonia, and respiratory dysfunction are major contributors to morbidity and mortality in PWS. It is clear that GH therapy improves lean body mass;

however, perhaps of greatest importance to children with PWS and their families is the hope that these changes will be accompanied by improvements in physical strength and function.

Over the years, anecdotal reports of improvements in physical stamina, strength, and agility have been reported in association with GH treatment of children with PWS.<sup>76</sup> Parental reports include a variety of new gross motor skills—e.g., independently climbing up the school bus steps, carrying a gallon carton of milk at the grocery store, participating in a normal gym class without restrictions, being able to join a karate class.<sup>37</sup> However, few studies have been conducted to quantify changes in physical performance.

In an uncontrolled interview study of 12 children with PWS treated with GH, all parents reported improvements in increased physical performance and activity; this effect was judged to be the most important clinical result of treatment.<sup>37</sup> In four children with PWS treated for 1 year, significant improvements in peak and mean power were demonstrated using an ergometer.<sup>40</sup>

Improvements in physical strength and agility were carefully documented in a previously described study<sup>26</sup> using objective measures, including a timed run, sit-ups, and weight lifting. Significant improvements in running speed, broad jump distance, number of sit-ups, and number of arm curls were documented after 12 months of GH treatment compared with controls. During 48 months of GH treatment, improvements in broad jumping and sit-ups were maintained, while further improvements were noted in running speed and arm curls. Despite the fact that the PWS children still scored well below the non-PWS children for all parameters studied, the improvements in strength and agility were associated with “real-life” functional benefits.

Similar positive results on body composition and resting energy expenditure have been reported in a 12-month double-blind, placebo-controlled, randomized crossover GH treatment study of 12 children with PWS.<sup>55</sup>

As reviewed in a previous chapter, the etiology of respiratory disorders in PWS has not been completely defined; however chest wall and oropharyngeal hypotonia are likely to be major contributing factors. Significant improvements in minute ventilation, airway occlusion pressure, and ventilatory response to CO<sup>2</sup> were reported after 6 to 9 months of GH treatment in nine children with PWS.

In the randomized, crossover study mentioned above,<sup>55</sup> significant improvements in peak flow rate, vital capacity, and forced expiratory flow rate were observed after 6 months of GH treatment. In addition, the number and duration of apneic events tended to decline.

In 20 children with PWS involved in a longitudinal study of GH therapy,<sup>26</sup> significant improvements in respiratory function were seen after 1 year of therapy and were sustained at retesting after 24 months of therapy.<sup>88</sup>

Figures 7.1 through 7.9 show the physiological effects of GH deficiency, GH therapy, and weight control successes and failures in various individuals with PWS (photos courtesy of their families).

### Behavioral and Psychosocial Effects

Few studies have addressed the effects of GH therapy on behavior and quality of life in patients with PWS, although parents and guardians often offer anecdotal reports of improvement, particularly in relation to eating behavior, alertness, and ability to concentrate. In addition, one might suspect that improved motor function would be associated with improvements in school performance and social functioning. The impression of increased alertness and activity has been reported in uncontrolled studies of GH therapy in PWS.<sup>40</sup>

Whitman et al.<sup>120</sup> have presented the most comprehensive study of behavioral parameters during GH therapy, as part of a controlled study of GH therapy in children with PWS. The behavioral component of this study involved 27 children receiving GH treatment and 14 control subjects studied using a modified Offord Survey Diagnostic Instrument. This instrument includes a behavioral checklist section and a parental questionnaire section. On the checklist section, no statistically significant between-group effects, positive or negative, were noted for multiple measures of psychological and behavioral function. However, within-group analysis showed a significant reduction of depressive symptoms only in the GH treatment group. In the under-11-year-old group, a significant increase in “attention-deficit/hyperactivity” symptoms was observed, perhaps in agreement with the anecdotal reports of increased alertness. In the questionnaire section, parents reported improved school performance, memory, and family/social relationships with GH therapy.

### Infants

Infants with PWS often suffer considerable morbidity related to hypotonia and respiratory disorders. Increased body fat and decreased lean mass have also been demonstrated, even in infants who are underweight.<sup>39,119</sup> However, deficits in linear growth may not be evident until after 12 to 24 months of age. In addition, questions regarding the safety and efficacy of GH therapy in severely hypotonic infants have been raised and gained further prominence with two reports of deaths of infants treated with GH.<sup>44,90</sup> For these reasons, studies of GH therapy in infants with PWS have received particular interest.

In a study of 11 children with PWS under 2 years of age, Eiholzer et al.<sup>42</sup> reported significant improvements in lean body mass (estimated by stable isotope dilution) and stabilization of fat mass compared with a group of six infants receiving only CoQ10 therapy over a 1-year period. Continued improvements in lean mass were observed over a 30-month GH treatment period. The same investigators have reported accelerated psychomotor development in infants treated with GH,

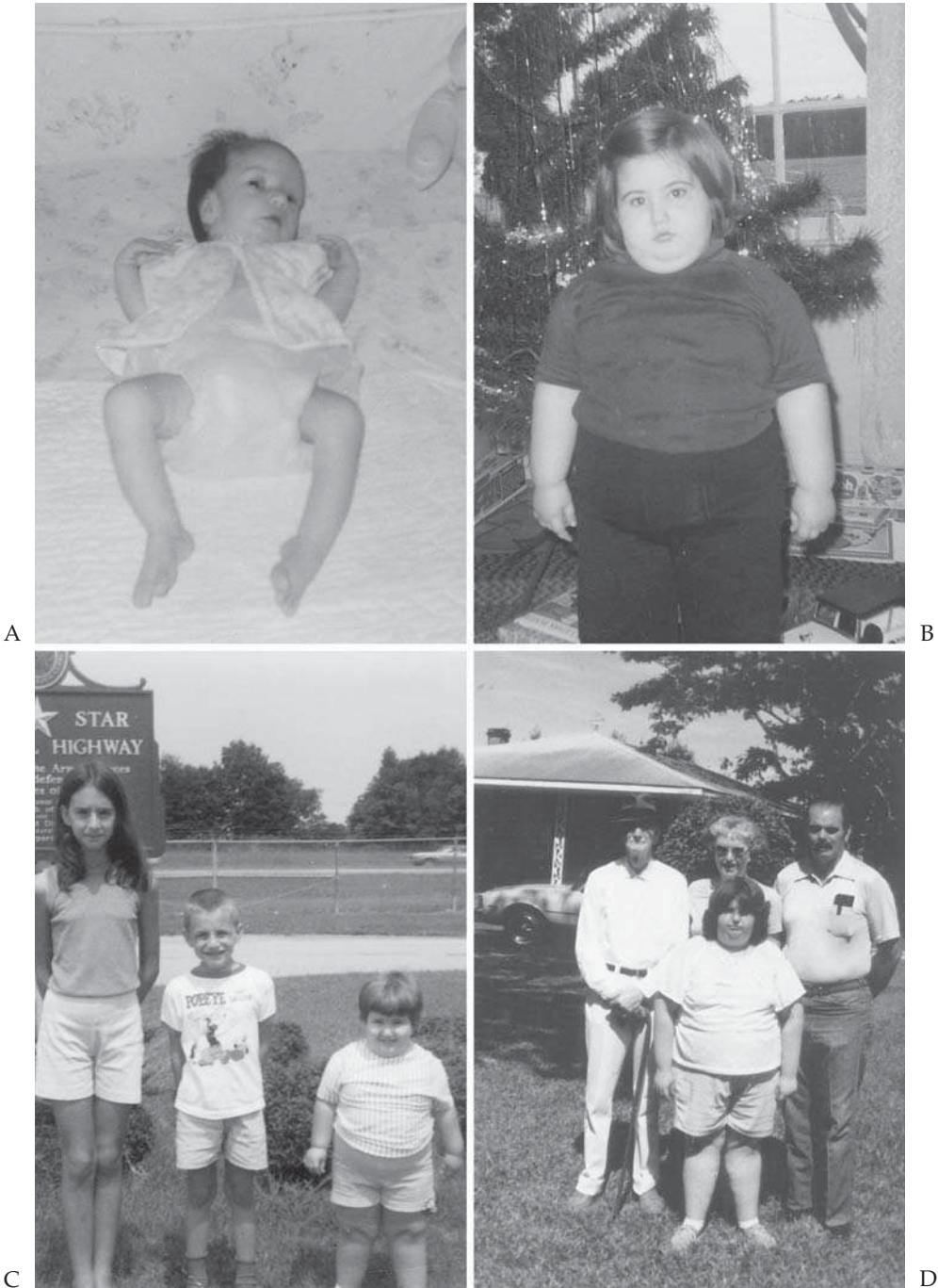


**Figure 7.1.** Female with PWS not treated with GH: adult height 4 ft. 11 ins.; maximum weight 310 lbs. **A.** Age 1.5 months. **B.** Age 3.5 years, before being diagnosed with congestive heart failure and pneumonia. **C.** Age 4, with older siblings. **D.** Age 16, with mother and maternal relatives.





E



F



G



H

**Figure 7.1.** E. Age 21, with male with PWS not treated with GH. F. Age 24. G. Age 28, with parents and older brother. H. Age 31, 1.5 years before her death.



**Figure 7.2.** Female with PWS not treated with GH: adult height 4 ft. 10 ins.; maximum weight 118 lbs. A. Age ~14 years. B. Age 28 years. C. Age 32 years. D. Age 34 years.





**Figure 7.3.** Male with PWS, not treated with GH but with controlled weight over lifetime. **A.** Age 9 weeks. **B.** Age 17 months. **C.** Age 2.5 years. **D.** Age 4.5 years. **E.** Age 12 years. **F.** Age 19 years.

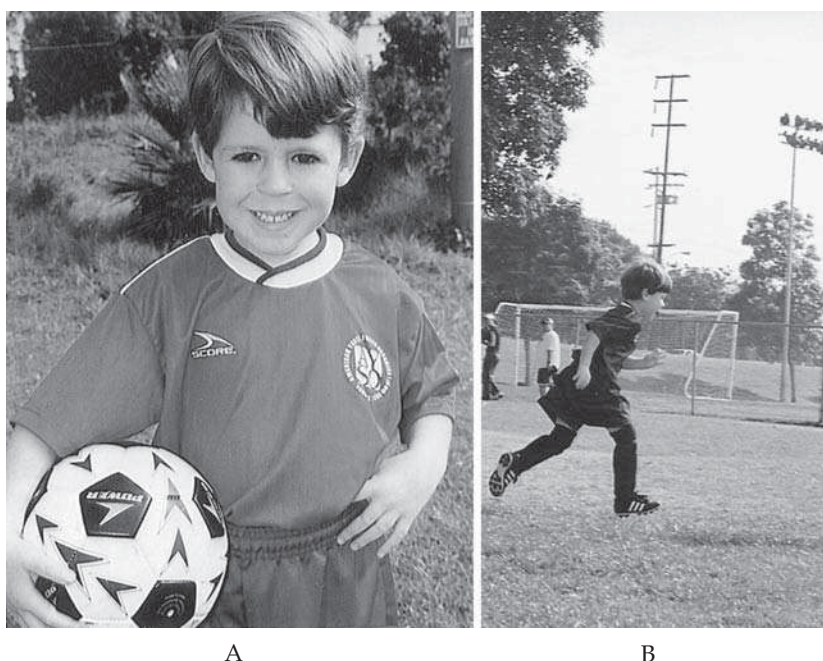


**Figure 7.4.** Male with PWS, treated with GH from age 9 months. **A.** Age 4, height ~42 ins., weight 37lbs. **B.** Age 4, playing soccer with nondisabled children.

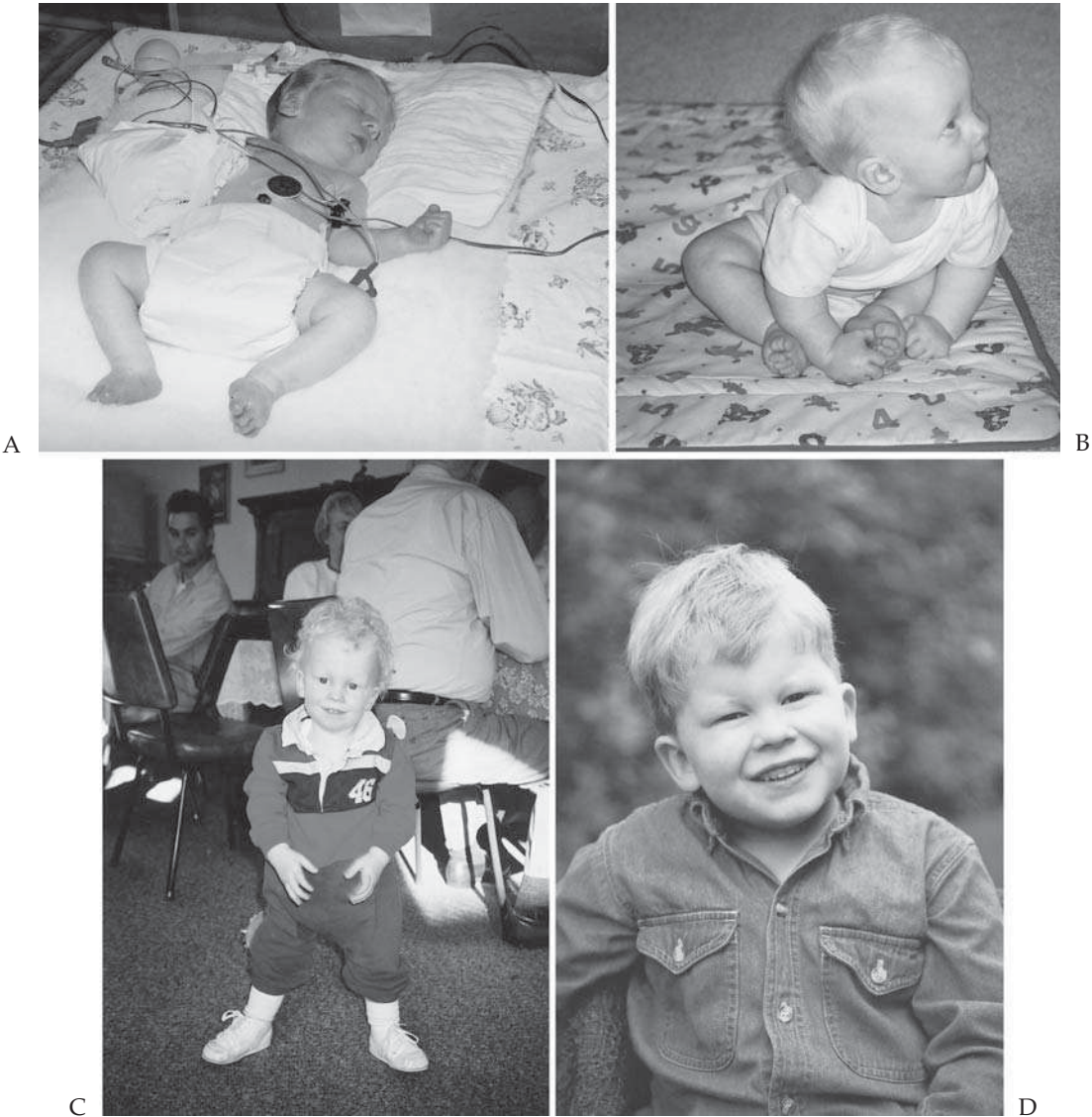


**Figure 7.5.** Male with PWS, treated with GH from age 8 years. **A.** Newborn. **B.** Age 10 months. **C.** Age 2 years. **D.** Age 5 years.





**Figure 7.5.** E. Age 8 years, at start of GH treatment; height 46.5 ins., weight 69.5 lbs. F. Age 9 years, after 12 months of GH treatment; height 51 ins., weight 73.5 lbs. G. Age 10 years, after 25 months of GH treatment; height 55.5 ins., weight 81 lbs. H. Age 11 years, after 36 months of GH treatment; height 58.5 ins., weight 90 lbs.

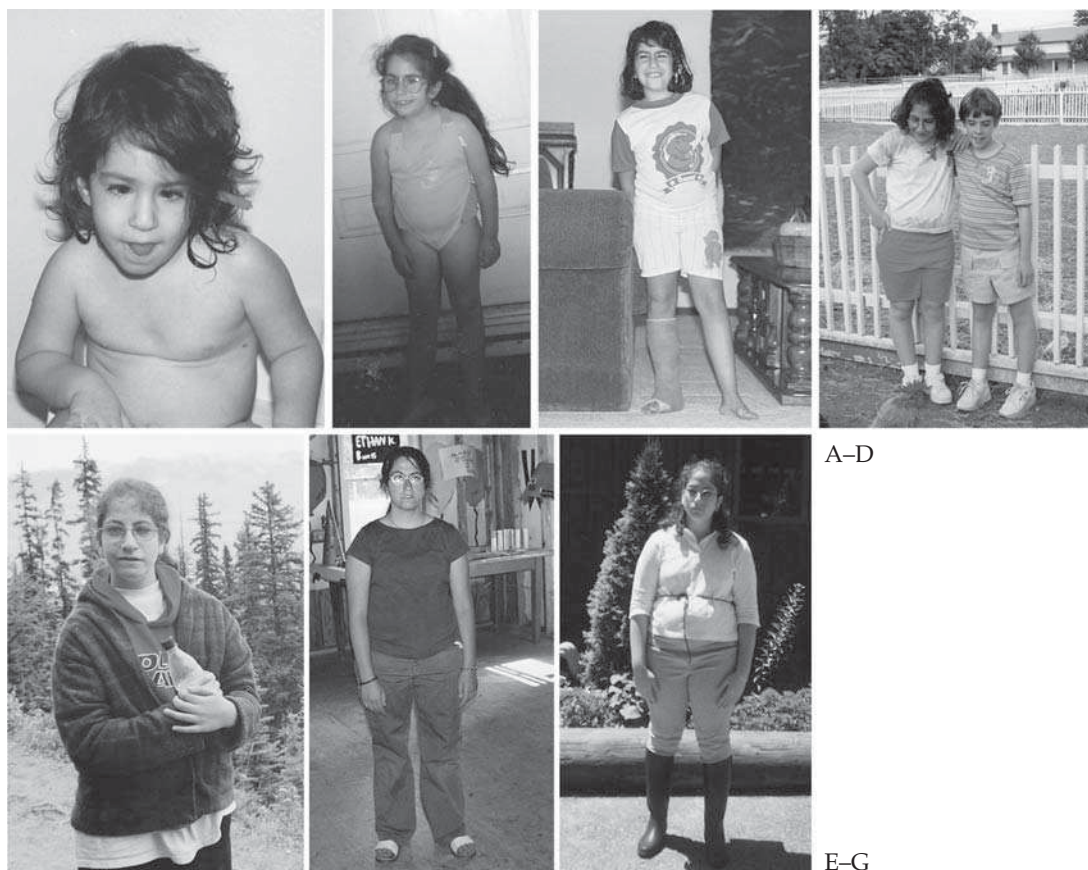


**Figure 7.6.** Female with PWS, treated with GH from age 7.5 to 14 years. **A.** Age 2.5 years. **B.** Age 5 years. **C.** Age 8 years, after start of GH. **D.** Age 12 (left), after 4+ years of GH, with 10-year-old treated female with PWS (shown also in Figure 7.7). **E.** Age 13, after 6+ years of GH. **F.** Age 14, after 7+ years of GH. **G.** Age 15 (in riding outfit), after stopping GH treatment.

which was attributed to improvements in muscle function.<sup>37,43</sup> No adverse effects of GH were noted during these studies.

In a randomized study (GH versus no-treatment) of 25 infants with PWS (mean age 15.5 months), a significant increase in lean mass and decrease in fat mass, both measured by DXA scan, was observed after 6 months of treatment.<sup>119</sup> In addition, age-equivalent motor scores increased approximately twice as fast in the treatment group, as measured by the Toddler Infant Motor Evaluation (TIME). Dramatic increases in head circumference within the normal range were noted in the treatment group with no evidence of CNS pathology; this increase presumably represents increased brain growth. No adverse effects were noted.

Based on these studies and composite experience, it is evident that GH therapy in infants with PWS is efficacious in improving growth, body composition, and neurodevelopment. No specific safety problems have been observed in the published studies. As discussed below, the cases of death reported during GH therapy are likely to be unrelated to GH therapy.



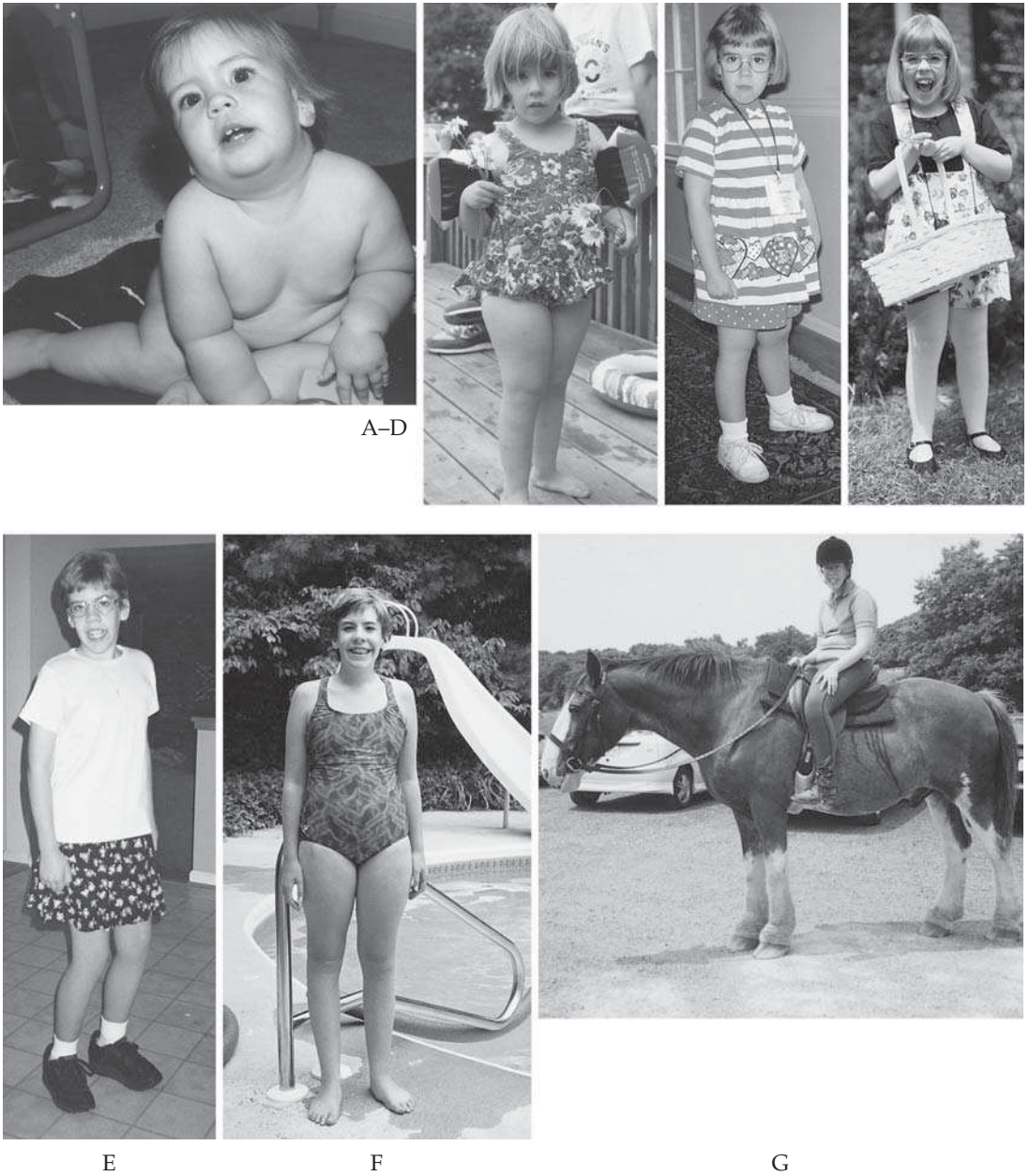


**Figure 7.7.** Female with PWS, treated with GH from age 9 years. **A.** Age ~11 months. **B.** Age 4.5 years. **C.** Age 6 years. **D.** Age 8.5 years, 6 months before start of GH treatment. **E.** Age 10 years, after ~2 years of GH treatment, wearing scoliosis brace. **F.** Age 13 years, after 4+ years of GH treatment. **G.** Age 15 years, height 5 ft. 5.5 ins., weight ~170 lbs., temporarily off GH before restarting at adult level.

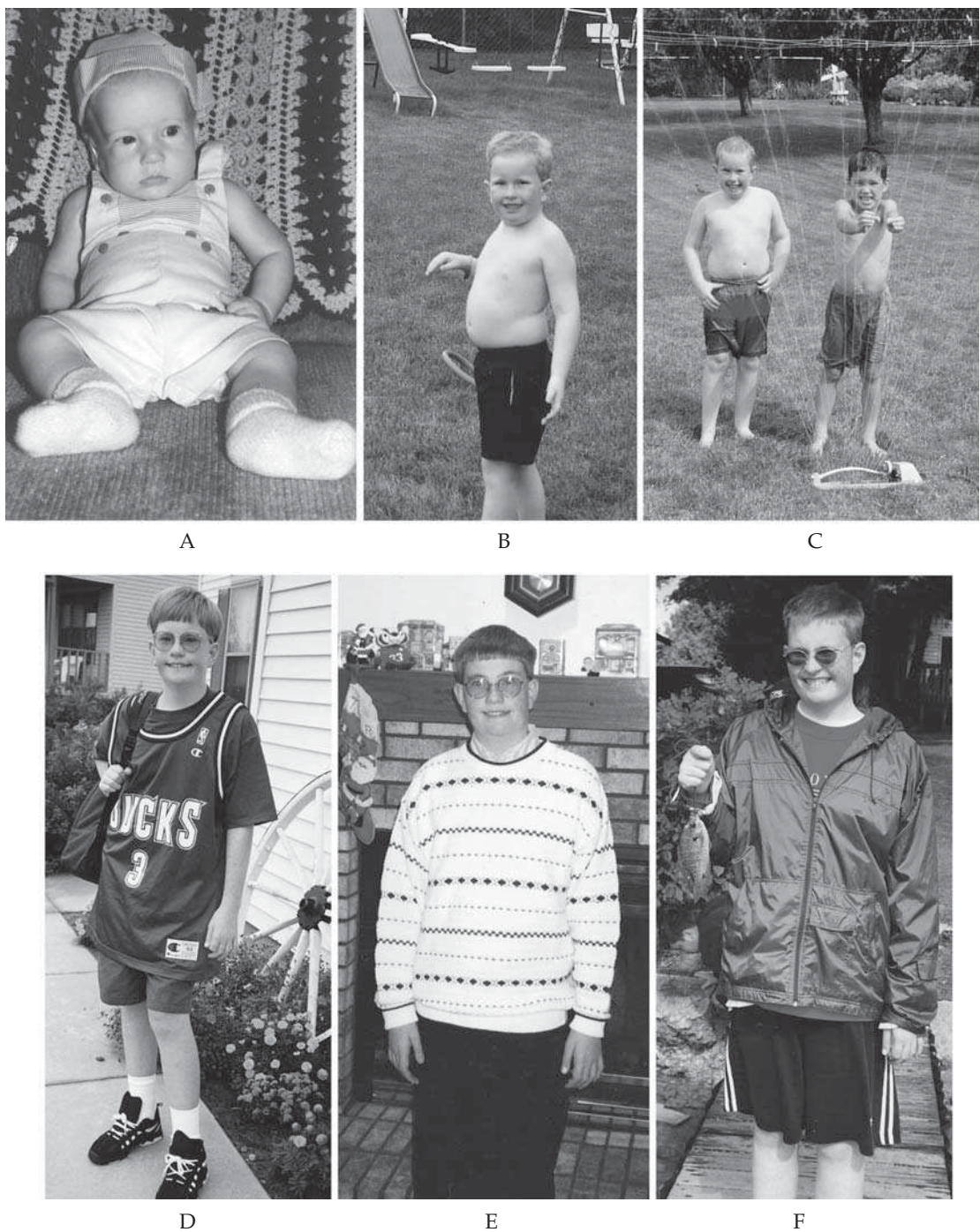


**Figure 7.8.** Male with PWS, treated with GH from age 11 years: **A.** Age 3 months. **B.** Age 3 years. **C.** Age 9 years (left), with 7-year-old sibling. **D.** Age 13 years, after 1.5 years of GH treatment. **E.** Age 15 years, after 3.5 years of GH (treatment then was stopped for 2 years). **F.** Age 18 years, after restarting GH at adult level 8 months earlier.



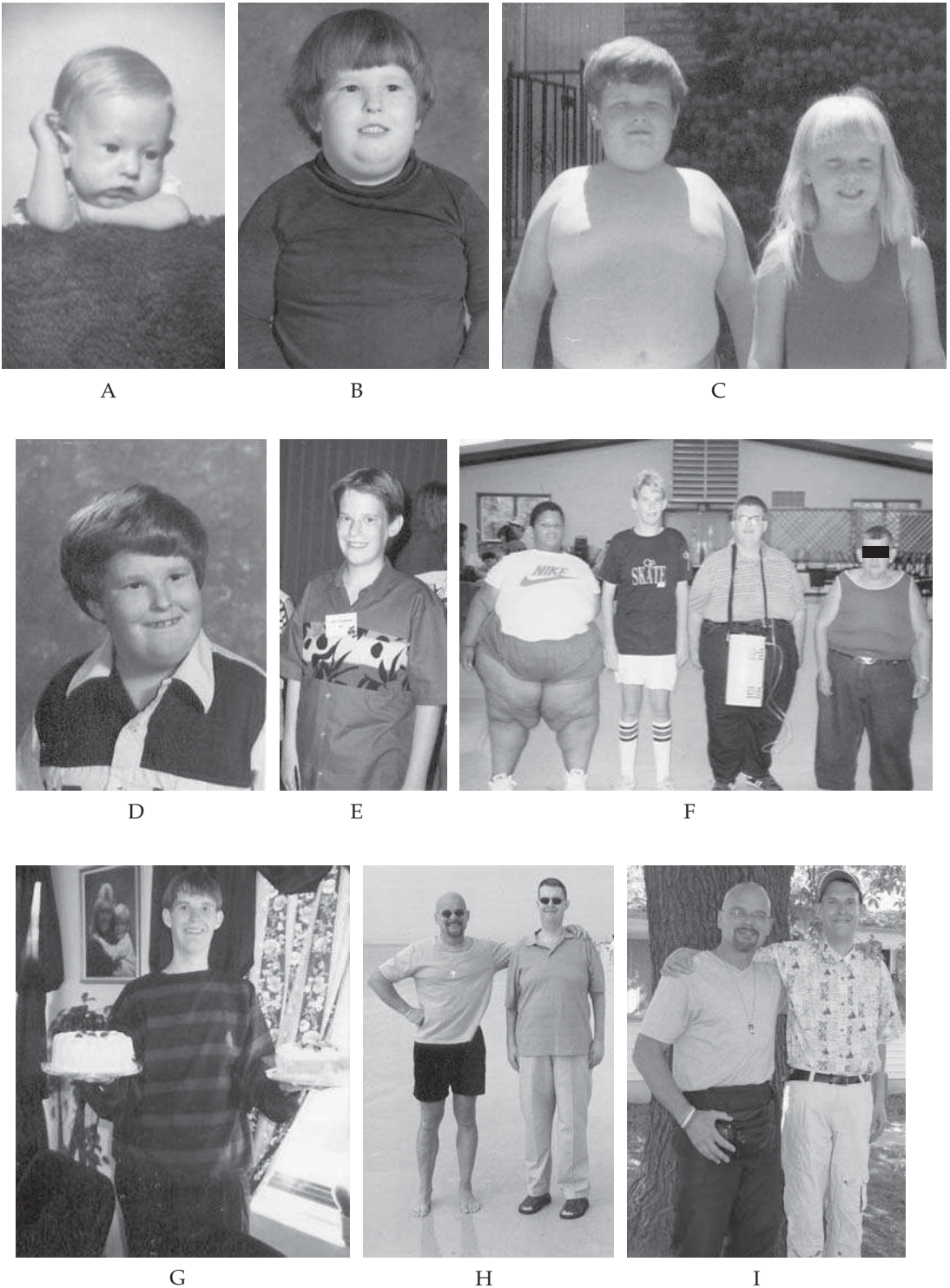


**Figure 7.9.** Male with PWS, treated with GH from age 14 years: **A.** Age 5 months. **B.** Age 4 years. **C.** Age 7 years, with sister age 6. **D.** Age 8 years. **E.** Age ~12 years, showing weight loss achieved through food management. **F.** Age 16 years (second from left), after 2 years of GH treatment, shown with three untreated males with PWS. **G.** Age 18, after 4 years of GH treatment. **H.** Age 30 (at right) with father, height 5 ft. 10 ins., weight 186 lbs., after discontinuing GH. **I.** Age 32 (at right) with father, weight 139 lbs., after restarting GH treatment.

## Adults

Knowledge of the natural medical course of adults with PWS is an evolving area of interest. Over the past decade, there has been an emphasis on earlier initiation of preventive interventions, more intensive and coordinated management of medical and psychosocial problems, and recognition and replacement therapy of GH deficiency.

Although linear bone growth is not a concern during adult life, detrimental effects of GH deficiency have been well documented in non-PWS adults with GH deficiency, including osteoporosis, increased body fat, decreased lean mass, increased risks for cardiovascular disease, fatigue, and psychological depression. In 1995, GH replacement therapy in adults with either childhood or adult-onset GH deficiency received regulatory approval from the U.S. Food and Drug Administration and in Europe. Numerous reports documenting the safety and efficacy of GH replacement in non-PWS GH-deficient adults have been published in the last decade<sup>115,116</sup> including large placebo-controlled, randomized clinical trials<sup>30,104</sup> and a growing number of multinational observational studies from surveillance databases (see below). As demonstrated in placebo-controlled randomized clinical trials, GH therapy improves body composition,<sup>6,35,65</sup> lipid profiles,<sup>52,65,115,116</sup> bone density,<sup>7,102</sup> and quality of life<sup>103</sup> in GH-deficient adults.

Recent studies indicate that adults with PWS have GH/IGF axis deficiency, as a continuation of the condition that begins in childhood.<sup>62,95</sup> In addition, several clinical features of adult PWS are similar to those observed in GH-deficient adults without PWS, and initial studies of therapy indicate similar treatment efficacy.<sup>61,63</sup>

The distinct psychosocial and clinical risk profiles in PWS suggest that GH replacement therapy could have unique benefits in this subpopulation of GH-deficient adults. In addition, there may be special considerations involved with GH replacement therapy in adults with PWS:

1. In contrast to most other individuals with childhood-onset GH deficiency, the majority of current PWS adults did not receive GH therapy as children. This raises concerns regarding potential side effects of initiating GH replacement therapy in treatment-naïve adults.
2. The presence of concomitant lifetime sex-steroid deficiencies could exacerbate the manifestations of GH deficiency.
3. The co-existence of significant medical conditions, including morbid obesity, scoliosis, insulin resistance, Type 2 diabetes mellitus (T2DM), and cardiovascular disease may occur at a relatively young age in PWS and require additional surveillance during GH treatment.
4. The effects of GH treatment on sleep apnea and other pulmonary problems in adults with PWS are uncertain.
5. Cognitive, behavioral, and social considerations could complicate both initiation and long-term administration of GH injections. The specialized living situations of many PWS individuals may be a limiting factor.

Thus, from a theoretical perspective, adults with PWS have a wider spectrum for both potential benefit and risk than do other adults with GH deficiency.

### Pretherapy Testing

Since most children with PWS will meet regulatory requirements for GH use, formal testing of GH secretion is not usually necessary prior to therapy. However, testing may be indicated in a few instances:

1. In the U.S., GH therapy is specifically labeled for treatment of PWS *with growth failure*, rather than for body composition abnormalities associated with PWS. In some cases, growth failure per se may be difficult to document. For instance, as previously described, children with PWS and premature adrenarche may have relatively accelerated linear growth, but compromised final height. In such cases, GH testing may be useful to document the alternate therapeutic indication of GH deficiency.

2. *In utero* and neonatal problems, including prematurity and hypoxia, are known risk factors for panhypopituitarism (i.e., GH deficiency plus other pituitary hormone deficiencies, such as TSH and ACTH). Infants with PWS who suffer these types of problems should be considered for a complete pituitary evaluation, including direct measurement of GH levels, since replacement of GH and other hormones may be necessary before the clinical development of “growth failure.” Unexpected neonatal hypoglycemia may be a warning sign of hypopituitarism; low GH and/or cortisol levels measured during hypoglycemia can be diagnostic for pituitary deficiency.

Another problematic situation is the neonate with PWS. Since evidence suggests that GH replacement may be beneficial for brain growth and neuromotor development, it may be clinically unwise to withhold therapy while awaiting documentation of growth failure. Consultation with a pediatric endocrinologist with experience in the treatment of neonatal PWS is highly recommended.

Other specific testing that may be considered for children with PWS prior to therapy includes the following:

1. Thyroid function testing (T4, TSH). Although thyroid abnormalities do not occur with increased frequency in PWS, thyroid problems are common in the general population and, if untreated, may have detrimental effects on neonatal development as well as limit the efficacy of GH therapy at all ages.

2. Fasting blood glucose and/or glycated hemoglobin (hemoglobin A1c). Elevations in either of these levels may indicate impaired glucose tolerance or Type 2 diabetes mellitus, either of which may be exacerbated by GH therapy.

3. Bone age radiograph may be useful to assess final height potential, particularly if the bone age is >6 years.

4. Liver enzymes to assess for hepatic steatosis and renal function tests (urea nitrogen and creatinine), if clinically indicated.

5. DXA scan to assess hip and spine density (standards generally not available below 8 years of age at the time of this writing), preferably in combination with a whole-body DXA scan to assess body composition.

6. Scoliosis radiographs, if clinically indicated (see discussion in Chapter 5).

Whenever feasible, formal baseline testing of motor function should be documented for comparison purposes. Video documentation may also be considered.

Since GH replacement therapy does not yet have specific regulatory labeling for treatment of adult PWS, formal testing of the GH/IGF axis GH secretion is necessary, despite the controversies regarding the physiologic relevance of stimulatory testing (as discussed in a preceding section). Results of population-based studies suggest that the measurement of IGF-I might be a useful initial screening test to detect abnormalities in the GH/IGF axis in young adults.<sup>2,84</sup> While the presence of a normal IGF-I does not rule out GH deficiency, the finding of a level that is below the age-specific normal range strongly suggests the possibility of this diagnosis. Because IGF-I levels naturally decline with age, a low level is more likely to indicate GH deficiency in younger, as compared with older, adults. Therefore, a two-stage screening procedure using an initial IGF-I determination followed by formal provocative GH testing could be a useful and cost-effective method to identify GH deficiency in young adults with PWS. The IGF-I screening procedure in older adults with PWS may be less sensitive and specific; however, since GH therapy in adults is guided by monitoring of IGF-I levels, measurement of this level prior to GH testing and/or GH therapy is recommended.

At the current time, there is considerable controversy regarding the optimal agent to use for provocative GH testing in adults.<sup>8,13</sup> Pro and con arguments relating to safety, validity, reliability (reproducibility), and cost can be given for virtually all secretagogues commonly used, including clonidine, L-DOPA, propranolol, pyridostigmine, arginine, GH-releasing factor and analogues, and insulin. Secretagogue selection is further complicated in adults with PWS in view of the potential interaction of obesity, gonadal steroid deficiency, and the presumed hypothalamic level of the GH secretory defect.<sup>112</sup> Insights gleaned from an increasing body of information based on studies of secretagogues in normal adults,<sup>9</sup> non-GH-deficient obese adults,<sup>107</sup> individuals with PWS,<sup>10,21,53,54,110</sup> and adults with presumed hypothalamic GH deficiency<sup>110</sup> suggest that L-DOPA may be the most effective and, perhaps, safest GH provocative agent in adult PWS.

The exact mechanism of GH deficiency in PWS, while not definitively ascertained, is often attributed to a hypothalamic defect, perhaps via a deficiency of GH-releasing factor (see preceding sections for further discussion). Recent publications suggest that L-DOPA and other dopaminergic stimuli may act to stimulate pituitary GH secretion by augmenting hypothalamic production or release of GH-releasing factor,

in contradistinction to another commonly used secretagogue, arginine.<sup>105</sup> The data further suggest that arginine increases GH secretion as a consequence of inhibiting hypothalamic somatostatin release in addition to having a direct stimulatory action on pituitary somatotrophs. This information, collected in non-PWS adults, suggests that L-DOPA and similar secretagogues that act at the hypothalamic level may be preferable to agents such as arginine, which have actions below the hypothalamic level, if the intent is to detect a defect in GH-releasing factor, as may be the case with PWS.

Arguing against the use of L-DOPA is the possibility of false positive (i.e., false low) results. In a study of 22 non-PWS, normal volunteers, one subject failed to respond to L-DOPA.<sup>9</sup> Several studies have shown blunted GH secretory response in association with increased adiposity in non-PWS adults.<sup>71,107</sup> Therefore, a second stimulation test or sequential testing might be useful in documenting or confirming GH deficiency in obese adults, such as those with PWS. However, an argument can be made for single-agent testing in adults who have a low IGF-I level and other clinical evidence consistent with GH deficiency.

In a typical provocative GH test, the subject is studied after an overnight fast (recent carbohydrate intake may inhibit GH secretion). A baseline sample is drawn, followed by administration of the provocative agent and timed serum sampling for a period thereafter.<sup>51</sup> A normal response is defined as a peak GH level above a selected level. Unfortunately, there is considerable disagreement regarding a diagnostic cutoff level in both children and adults. While a peak level of less than 3 to 5 mcg/L is generally accepted as an indication of GH deficiency, some experts have advocated higher boundary levels of up to 15 mcg/L. Therefore, the interpretation of results from a provocative GH test should be interpreted in conjunction with IGF-I and/or IGFBP-3 levels and clinical signs and symptoms.

For adults with PWS, other recommended tests prior to GH therapy are similar to those listed above for children with PWS, with these exceptions/additions:

1. Bone age radiographs are not indicated in adults since they have already achieved epiphyseal closure.
2. On the other hand, since scoliosis may progress during adult life, appropriate radiographs should be obtained, if clinically indicated.
3. IGF-I levels, used for therapeutic monitoring, should be obtained at baseline.
4. Because height growth cannot be used as a somatic efficacy measure, a baseline DXA scan, preferably with measurement of whole body composition in addition to hip/spine bone mineral density, is highly recommended.
5. Adults may be at an increased risk for glucose intolerance and Type 2 diabetes mellitus. Therefore, consideration should be given to inclusion of an oral glucose test prior to initiation of GH therapy.



6. Consideration should be given to a baseline prostate-specific antigen (PSA) level in males and PAP smears and mammograms in females.
7. A baseline quality-of-life assessment may also be useful.

### Childhood GH Therapy

In a general sense, GH therapy for children with PWS follows the same course as for other conditions. Monitoring of linear growth, growth potential (e.g., via bone age radiographs), and weight serve as the primary indicators of therapeutic effect and the need for dose adjustment. However, while somatic growth is an important effect of therapy, the beneficial effects of GH on body composition and physical function are of greater importance in children with PWS. In this sense, height growth serves primarily as an obvious surrogate marker for overall therapeutic efficacy, including body composition.

Currently, labeling for GH use in children with PWS states that “Generally, a dose of 0.24 mg/kg body weight/week is recommended” (full prescribing information at [www.genotropin.com](http://www.genotropin.com)), or 0.034 mg/kg/day. The European labeling for Genotropin/Genotonorm includes the alternate dose calculation of 1.0 mg/m<sup>2</sup>/day based on body surface area. This recommendation is apparently based on data from Europe, where GH doses used are generally lower than in the U.S. for all treated conditions. In a review of 15 sets of studies relating to GH use in PWS, Eiholzer<sup>37</sup> found doses ranging from 0.02 to 0.05 mg/kg/day. The highest reported doses (0.04–0.05 mg/kg/day) were those from some of the earliest studies,<sup>3,4,56,74</sup> and one of the authors (PDKL) has continued to use a standard dose of 0.05 mg/kg/day for all pediatric patients with PWS. Another author (ALC) has co-authored studies regarding GH dose-response in PWS,<sup>26</sup> as described in a preceding section of this chapter.

Controversy over GH dosage in PWS is mirrored by similar discussions in non-PWS conditions that have endured for many decades.<sup>49,66</sup> Although GH therapy has been in use for over 40 years and synthetic GH was released in 1985, surprisingly few data have been published regarding optimal dosage for any condition. In most studies related to dose response, the maximal measured response occurs at the highest dose tested, which is the case in relation to GH effects on body composition in children with PWS.<sup>26</sup> Even for a straightforward endpoint such as height growth in non-PWS GH-deficient children, optimal dosage has not been defined, although it is clear that for a given weekly dosage, daily administration is more efficacious than a less frequent dose interval and that increased efficacy is not necessarily proportionate to increased dose.<sup>49,66</sup> Indeed, the average dose used for treatment of childhood GH deficiency, 0.3 mg/kg/week (0.043 mg/kg/day), seems to have evolved primarily from composite practice experience and is higher than at least one manufacturer’s recommendation (0.16–0.24 mg/kg/week, [www.genotropin.com](http://www.genotropin.com)). In addition, this dose is approximately three times the weekly dose used prior to the availability of synthetic GH and three times the estimated physiologic GH secretion rate for normal children. Higher weight-based doses have



been recommended for children with Turner syndrome (0.375 mg/kg/week), growth failure associated with chronic renal failure (0.35 mg/kg/week), small-for-gestational-age children with failure of catch-up growth (0.48 mg/kg/week), and for “pubertal dosing” of GH-deficient children (0.7 mg/kg/week).

Efforts to define individualized upper-dose limits based on IGF-I levels are complicated by high interassay and interlab variability, intra-individual physiologic variability, age- and sex-dependent normal ranges, and extremely wide normal ranges, especially during puberty. In addition, long-term efficacy data based on IGF-I or other biochemical response markers are not available. There are virtually no data relating adverse effects to doses within the usual prescribed ranges.<sup>66</sup> For PWS, an argument has been made that dosing should be based on lean mass rather than on total body weight. However, this would require accurate determination of lean mass at each visit and, more importantly, there are no data to support the effectiveness of such an approach.

A prudent approach to GH therapy in children with PWS may be to use a dose that is at least at the labeled recommendation of 0.24 mg/kg/week (0.034 mg/kg/day, based on total body weight) but not to exceed the highest published efficacious dose (0.35 mg/kg/week, or 0.05 mg/kg/day). The Genotropin/Genotorm package labeling includes a warning that “Daily doses of 2.7 mg should not be exceeded.” The authors recommend consultation with a pediatric endocrinologist with experience in PWS treatment when initiating GH therapy for an individual with PWS.

As mentioned above, height is a reasonable measure of clinical efficacy in children with PWS. As observed in other GH-treated populations, for a given weight-based dose the height velocity will be greatest during the first year of therapy, typically into supranormal ranges; this may be due to “catch-up” growth. This is often followed by a decrease into essentially normal height velocity ranges, transient augmentation with initial sex-steroid replacement, and eventual attainment of a final adult height.

Other clinical parameters that should be monitored during childhood GH therapy include the following:

1. Weight, body mass index, body fat: Although numerous studies indicate that GH therapy may significantly reduce body fat in children with PWS, this effect is not universal. GH therapy may actually augment accretion of body fat in children who do not have a controlled diet.

2. Head circumference: Infants with PWS may have an initial preferential growth in head circumference. Failure of head growth should raise suspicions of craniosynostosis, especially if the fontanelles are prematurely closed; this disorder requires immediate evaluation. In cases with an exuberant increase in head growth, hydrocephalus can usually be excluded by careful clinical examination. Widely-spaced sutures and/or a bulging anterior fontanel should be cause for concern and further evaluation.

3. Back curvature: As discussed in Chapter 5, scoliosis is a common occurrence in PWS, and an abnormal curve may worsen during rapid growth. It should be emphasized that GH therapy is not thought to cause scoliosis in PWS, and there is no current evidence for stopping GH therapy because of this condition. Close coordination with orthopedic care is needed. A significant scoliotic curve should also be taken into account when monitoring height.

4. Bone age radiograph: An annual hand/wrist radiograph for determination of bone age was formerly a standard practice during childhood GH treatment. The primary utility of a bone age is for estimation of epiphyseal closure and further growth potential (i.e., final adult height potential). To avoid unnecessary radiation exposure, it may be best to limit bone age radiographs to situations where there is a concern regarding further growth potential. It should also be remembered that height is determined by growth of the vertebrae, hips, and legs—these epiphyses typically close after those of the hand. Therefore, bone age radiographs should always be interpreted together with actual measurements of height velocity.

5. DXA: Although DXA provides useful research information regarding changes in body composition, its role in clinical monitoring of childhood GH therapy is not clear. Hip and vertebral measurements are useful for diagnosing and monitoring osteoporosis, particularly for adolescents and young adults. The clinical utility of whole body DXA is currently under investigation.

6. Laboratory testing: At the current time, there is no evidence to support *routine* monitoring of IGF-I, IGFBP-3, thyroid function tests, glucose tolerance, hemoglobin A1c, or other laboratory tests during GH therapy of children with PWS. Of course, such tests may be indicated in individual cases based on signs and symptoms, and an individual physician may have his or her own routine monitoring guidelines based on personal experience and opinion.

7. Whenever possible, muscle function, physical activity, school performance, and quality-of-life measures should be monitored.

Childhood GH therapy is usually continued until attainment of final adult height. It should be noted that height growth may continue after apparent closure of hand and wrist epiphyseal centers (i.e., on a typical bone age radiograph), since the hip, knee, and vertebral epiphyses tend to mature more slowly than the distal centers. Patients are usually seen in clinic at 3- to 4-month intervals for dose adjustments and monitoring. Lack of significant height gain (after correcting for the effects of scoliosis) over two visit intervals (or approximately 6 to 8 months) may be an indication for cessation of childhood GH therapy and consideration for transitioning to the adult GH therapy regimen. The issue of how to optimally transition GH-deficient individuals from childhood to adult therapy is somewhat controversial, with some practitioners recommending immediate transitioning and others advocating cessation of GH therapy and periodic reevaluation of GH/IGF status and body composition.<sup>106</sup> Limited experience suggests that individuals with PWS have a rapid reversal of body composition benefits with GH

cessation; therefore, long-term GH withdrawal cannot be recommended. In all cases, careful monitoring during the transition period is essential.

### Adult GH Therapy

As with non-PWS adults,<sup>33</sup> the goals of GH therapy in adults with PWS include improvements in (1) body composition, with reduction of fat mass and increase in lean mass; (2) lipid profiles; (3) bone density; and (4) quality of life. In addition, as with treatment of children with PWS, improvement in muscle function is also a desirable outcome.

In contrast to childhood GH therapy, where GH dosing is based primarily on body size (weight or surface area) and growth response, GH dosing in adults is more typically administered in a fixed amount (mg/day) with adjustments based on laboratory measures of response. In adult patients with adequate nutritional status and normal liver function, the serum IGF-I level is considered to be the best clinical surrogate measure of GH adequacy.

For adults with GH deficiency, a typical starting dose is 0.1 to 0.2 mg/day, without adjustment for weight or surface area. (Note that when corrected for a typical adult weight, this dose is several-fold lower than in children). Subsequent dose changes are often based on routine measurements of IGF-I at 1- to 6-month intervals, with GH dose changes in 0.1- to 0.2-mg/day increments/decrements to achieve an IGF-I level within 0 to +1 standard deviation of age- and sex-specific normal ranges. Experience suggests that a typical stable dose to maintain normal IGF-I levels is 0.6 to 1.0 mg/day for adults with PWS.

In general, IGF-I should be measured approximately 1 month after a GH dose change. It should be noted that IGF-I levels show considerable variability based on assay methodology and laboratory. Therefore, it is important to select a single laboratory with good reference ranges and quality control procedures.

Other parameters to be monitored during adult GH therapy include the following:

1. Weight, BMI, body fat—For the same reasons as stated for children. Bioelectrical impedance assessment can provide a reasonably objective estimate of body fat, as discussed in the preceding chapter.
2. Back curvature.
3. DXA—Osteoporosis is a major cause of morbidity in adults with PWS; therefore, regular measurements (every 1 to 2 years) of hip and spine bone mineral density are recommended. Whole body DXA may provide useful estimates of body composition, as described in the preceding chapter.
4. Polysomnography and/or pulmonary function testing may be indicated in individual cases, as discussed in Chapter 5.
5. Laboratory testing—Annual fasting lipid panel, fasting glucose, hemoglobin A1c, and general chemistry profile (including liver enzymes) may be recommended, especially for very obese patients and/or those with uncontrolled excessive weight gain. More frequent

monitoring may be needed in the first few months of therapy and for those patients with known T2DM, dyslipidemia, or hepatic steatosis.

6. Hemoglobin and hematocrit may also be included in the routine monitoring for menstruating women.

7. As mentioned above, IGF-I levels should be monitored as a surrogate measure of GH adequacy. Whenever possible, physical activity, job performance, psychological status and quality of life should be monitored. In selected patients, cardiology evaluations (echocardiogram, treadmill stress test) may be indicated.

Treatment of adult GH deficiency is presumably a lifelong necessity. However, there are no long-term, randomized, placebo-controlled studies of GH replacement in adults; therefore, clinical experience is an essential element for guiding therapy. Adult patients receiving GH therapy can be followed less frequently than children, perhaps at 4- to 6-month intervals.

### **Safety and Contraindications**

There are no long-term, randomized, placebo-controlled studies of GH therapy in any population. Safety and efficacy monitoring of adult GH replacement therapy is based primarily on observational data from large post-marketing surveillance databases,<sup>5,87,100</sup> which together contain tens of thousands of patient years of treatment experience. Despite the intrinsic methodological limitations of such studies due to the absence of a comparison (control) arm, these databases suggest that GH replacement is safe and confers distinct clinical benefits when administered in appropriate doses. Nevertheless, health care professionals should be aware of potential adverse events during GH therapy.

As described in preceding sections, GH therapy during childhood may be associated with changes in physical features and body proportions (faces, hands, feet) due to bone growth and remodeling. In children with PWS, these changes generally lead to a “normalization” of body features and are not considered adverse effects. However, after epiphyseal closure, continued treatment at childhood dose levels can lead to a coarsening of features and bone overgrowth, as is observed in acromegaly. Therefore, it is important to monitor the response to GH during childhood and transition to adult dosage when long bone growth has ceased.

Scoliosis is a common, progressive condition in PWS, regardless of GH therapy. Therefore, all children and adults with PWS should have regular monitoring of back curvature and appropriate orthopedic monitoring and treatment. Progression of scoliosis may worsen during rapid growth, such as during a pubertal growth spurt or, theoretically, with childhood GH or gonadal steroid therapy. However, studies have not shown an independent effect of GH therapy on progression in PWS.<sup>79,81</sup> Anecdotal reports from experienced orthopedists indicate that GH therapy may improve bone quality and efficacy of surgical treatment for scoliosis.

Slipped capital femoral epiphysis (SCFE) is a childhood condition in which the femoral epiphyseal plate is dislocated posteriorly, resulting in hip (and referred) pain and an abnormal gait. This condition is known to be associated with non-PWS obesity and may also be associated with hypopituitarism, hypothyroidism, and GH therapy.<sup>123</sup> A survey study of 898 members of PWSA (USA) revealed only one case of SCFE among 565 respondents, suggesting a much lower than expected incidence.<sup>118</sup> However, since pain is a major presenting sign of SCFE and individuals with PWS are known to have an increased pain threshold, this could be an underestimate. Clinicians and other caretakers should be vigilant for abnormalities in gait that could signal a need for further evaluation.

GH deficiency is associated with decreased body water<sup>101</sup> and GH replacement therapy can be associated with acute retention of salt and water.<sup>122</sup> In both children and adults, this can manifest as pseudotumor cerebri or idiopathic intracranial hypertension,<sup>123</sup> which is associated with acute onset of headache, visual changes, gait disturbance, nausea, and dizziness. This condition is accompanied by papilledema and could lead to visual loss, although this complication would be unusual for GH-associated cases. Treatment involves cessation and/or lowering of the GH dose. As of this writing, there has been 1 reported case of pseudotumor cerebri in PWS,<sup>56</sup> which may be comparable to the observed risk of 1.6 cases per 1,000 patient years in GH-deficient non-PWS children.<sup>123</sup>

Another manifestation of GH-related salt and water retention is peripheral edema, which occurs almost exclusively in adult GH-treated patients. This complication is said to be the most common emergent complaint during GH replacement therapy in adults, and it was particularly frequent in early investigations when higher doses were administered. As with pseudotumor cerebri, treatment involves a lowering of the GH dose. Mild to moderate peripheral edema has been anecdotally observed in adults with PWS receiving GH therapy; however, the frequency of this adverse event has not been defined. Peripheral edema also was reported in 3 of 12 pediatric patients with PWS who received higher-dose GH therapy.<sup>79,81</sup>

GH therapy of non-PWS, pituitary GH deficiency often unmasks an underlying TSH deficiency, leading to deficiencies in T4 (thyroxine) and T3 (triiodothyronine). Therefore, measurement of thyroid hormone levels (T4, T3, and/or the free forms of these hormones) is recommended for true pituitary GH deficiency. However, this co-occurrence of GH and TSH deficiency has not been reported in PWS, and repeated studies have not shown an increased risk for hypothyroidism, either central (TSH deficiency) or peripheral (primary hypothyroidism) (see Medical Considerations chapter).

GH therapy can cause a decreased T4 level by increasing the conversion<sup>122</sup> of T4 to T3; in these cases, T4 will be low or low-normal, while TSH and T3 will be normal. Some clinicians choose to treat this condition with thyroxine, although there are no data to suggest treatment efficacy. This condition is often transient, even with continuation of GH therapy, and invariably resolves after cessation of GH

therapy. One suspected case of this occurrence has been reported in PWS.<sup>79</sup>

GH therapy can acutely decrease insulin sensitivity by counteracting endogenous insulin action. In cases where there is obesity preceding insulin resistance, and/or a genetic predisposition to insulin resistance, the addition of GH therapy can trigger the onset of T2DM. Furthermore, GH therapy could potentially worsen glycemic control in patients with poorly-controlled T2DM, although the longer-term effects on lean and fat mass may increase insulin sensitivity. Post-marketing surveillance databases indicate that this type of complication may be particularly frequent in GH-treated patients with Turner syndrome or intracranial tumors.<sup>122</sup> Increased frequency of GH-induced T2DM has not been formally reported in PWS; however, one of the authors (PDKL) has observed a few such cases, all of whom were very obese and had preceding evidence of insulin resistance or glucose intolerance. Cessation of GH treatment led to reversal of the T2DM, and subsequent weight control allowed restarting therapy at a lower dose without recurrence of T2DM. A worsening of well-controlled, pre-existing T2DM has not been observed with GH therapy. Some clinicians have anecdotally recommended that individuals with PWS not be given GH therapy if they have uncontrolled weight gain and/or are >200% of ideal body weight. GH therapy does not adversely affect carbohydrate metabolism in children with PWS who do not have preceding evidence for insulin resistance and/or glucose intolerance.<sup>69</sup>

The question of whether GH therapy may increase cancer risk has been raised based on limited data showing possible increases in risk for leukemia and colorectal cancer in GH-treated populations.<sup>92,122</sup> This concern is accentuated in PWS due to suggestions, albeit not proven, that there may be an increased overall risk for cancer (see Medical Considerations chapter). Ongoing analyses of post-marketing surveillance databases have not shown an increased risk for primary, secondary, or recurrent cancers in GH-treated individuals, including those with PWS.<sup>123</sup> GH is relatively contraindicated in conditions where there is a known risk for cancer, such as Bloom syndrome,<sup>122</sup> although it is not entirely clear that GH contributes to the risk. This contraindication cannot be logically applied to PWS, where the suggestion of an increased cancer risk has not been proven.

In 2002, Eiholzer and colleagues reported two cases of sudden death in children with PWS during GH treatment.<sup>44,90</sup> These cases and subsequent published reports<sup>117</sup> raised an international concern that GH therapy may increase mortality risk in children with PWS. A worldwide survey of GH-treated PWS patients through mid-2004 revealed a total of 13 cases of death in children, aged 0.7 to 16 years, treated for 2 weeks to 1.5 years. Although the cause of death was not definitely determined in all cases, respiratory compromise, often with concurrent pulmonary infection, seems to be a common link.

These cases spurred a worldwide interest in mortality in PWS. Published reports indicate that over the same approximate time period, there have been more than 30 deaths in children with PWS who were



not treated with GH,<sup>17,44,90,93,108,109,111,117</sup> and the authors are aware of additional unpublished cases. The cases with known cause of death are remarkably similar to those reported during GH therapy. A publication dated prior to regulatory labeling of GH for use in PWS advocated for collaboration to investigate the phenomenon of sudden death in PWS.<sup>108</sup>

Additional arguments against a relationship of GH therapy and risk of sudden death include (1) the absence of evidence for GH as a cause for increased contributory morbidity in PWS and (2) published studies showing that GH therapy improves respiratory function in PWS.<sup>55,82</sup> Moreover, the dose of GH is known for 11 of the 13 cases of death during GH therapy and all were relatively low, with only 2 individuals treated at or above the recommended level (0.24 and 0.26 mg/kg/week) and the remainder treated at >0.10 to 0.23 mg/kg/week. As of this writing, the relationship between GH treatment and mortality in PWS continues to be a subject of intense investigation. However, a logical conclusion based on current information might be that which was suggested by a statement in the first published report<sup>90</sup>: “The boy reported here . . . thus died before the effects of GH therapy could manifest themselves . . .”

Finally, there have been anecdotal concerns that GH therapy could exacerbate behavioral problems in children with PWS. However, detailed, objective behavioral studies conducted during a 2-year, controlled study of GH therapy in 41 children (27 treatment, 14 control) found no differences for measures of attentional symptoms, anxiety, obsessive-compulsive complex, violence, or psychotic symptoms.<sup>120</sup>

In summary, GH therapy in general has had a remarkable safety record. Adverse effects specifically observed in PWS are either reversible with cessation or reduction of GH therapy (water and salt retention, exacerbation of insulin resistance) or related to pre-existing conditions that require separate attention (scoliosis). Caretakers should be vigilant for the possibility of rare events, such as malignancy, and for complications that are usually signaled by pain in non-PWS conditions (SCFE, pseudotumor cerebri), although none of these complications have been reported to be specifically associated with GH treatment of PWS. Current concerns about the risk for sudden death in PWS are under investigation and a relationship to GH therapy is not supported by available data.

### Comprehensive Care

Traditional care guidelines for individuals with PWS, including many of those included in this text, are based on experience in non-GH-treated individuals. At the risk of oversimplifying, the major guidelines can be summarized as follows:

1. Strict dietary limitations to prevent overweight
2. Developmental, occupational, and educational therapy
3. Intensive physical therapy and exercise to counteract the hypotonia
4. Psychological/psychiatric evaluation and therapy

Although the above therapies have provided immeasurable benefits for countless individuals with PWS and their caretakers, they produce no substantial changes in the characteristic body habitus, limited muscle mass and function, or behavior. At each stage of life, a typical, distinctive “look” could be expected, as clearly depicted in the life-sequence pictures of non-GH-treated individuals included in this book and other references.<sup>37,70</sup>

As is also depicted in life-sequence photographs in this text and elsewhere,<sup>24,37</sup> GH therapy has resulted in a remarkable change in the appearance and physical function of individuals with PWS, alleviating many but not all of the associated morbidities as summarized in Table 7.1.<sup>72,73</sup> These changes are most dramatic for individuals treated with GH from a young age, but may also be important for adolescents and adults.

**Table 7.1. Morbidity and Treatment in Prader-Willi Syndrome**

| Morbidity                                           | Contributory Factors                                | Therapy                                                    |
|-----------------------------------------------------|-----------------------------------------------------|------------------------------------------------------------|
| Genital hypoplasia, cryptorchidism, hypogonadism    | Gonadotropin deficiency                             | Surgery, gonadal steroids                                  |
| Hypotonia                                           | GH/IGF deficiency, other factors not yet defined    | Physical therapy, GH                                       |
| Scoliosis                                           | ? hypotonia                                         | Orthopedic care                                            |
| Osteoporosis                                        | GH/IGF deficiency, hypogonadism                     | GH, gonadal steroids, bisphosphonates                      |
| Respiratory dysfunction                             | Hypotonia, ?central component                       | GH, surgery, and supportive care if clinically indicated   |
| Obesity (increased body fat, independent of weight) | Not fully defined                                   | Diet, exercise, GH                                         |
| Hyperphagia, overweight                             | Not fully defined                                   | Diet, exercise<br>? GH effect                              |
| Acromicria                                          | GH/IGF deficiency                                   | GH                                                         |
| Short stature                                       | GH/IGF deficiency                                   | GH                                                         |
| Insulin resistance, T2DM, related conditions        | Obesity                                             | Diet, exercise<br>? GH effect                              |
| Cognitive defect                                    | Not fully defined                                   | Behavioral and educational therapy                         |
| OCD-like behavior, psychosis                        | Not fully defined                                   | Psychotherapy ± psychotropic agents                        |
| Low academic and social functioning                 | Composite effect of physical and mental limitations | Behavioral, educational, and psycho-therapy<br>? GH effect |

For many of the morbidities, the full therapeutic effects of GH are not yet completely defined. GH may have a dual effect on the spectrum of disorders related to obesity, an acute exacerbation of insulin resistance, followed by increased insulin sensitivity as muscle mass increases; this possibility is currently under investigation. Although initial data indicate potential beneficial effects on psychosocial and behavioral function, long-term treatment outcomes have not been reported.

The improvements in physical appearance and function inevitably facilitate psychosocial integration and interactions. In addition, there may be increased resting and active energy expenditure related to increased muscle mass. Additionally, improved medical attention to gonadal steroid replacement may further enhance physical appearance and function. The implications of these changes for comprehensive care of PWS are not completely known, and are likely to be fully defined only with long-term follow-up of patients receiving GH and gonadal steroid replacement. However, as stated by an international consensus panel in 2001,<sup>36</sup> a comprehensive team approach to the individual with PWS is the most logical avenue for provision of optimal care (see Appendix B).

We end this chapter with a few of the additional medical care considerations that are introduced by hormone replacement recommendations:

- *Diet:* It is not clear at this time whether GH has a significant effect on hyperphagia, although experience suggests that dietary control remains a crucial element of care. However, calorie-guided diets must now take into account the increased requirements associated with GH therapy. Strict application of traditional PWS calorie limitations may lead to undernutrition. Weight, body composition, and, for children, growth should be carefully monitored.
- *Physical therapy and exercise:* Traditional expectations for improvement need to be raised and therapy should be individualized. For school-age children, mainstreaming into usual age-related physical education and selected other activities may be possible.
- *Cognitive function and behavior:* There is no current evidence that GH therapy improves cognitive abilities or behavior, although parents reported improvements in memory and school performance<sup>120</sup> in a controlled study of school-aged children. Therapists and educators should be aware that adherence to traditional assumptions of cognitive limitations may not be appropriate. On the other hand, normalization of physical appearance does not eliminate the need for proper attention to typical PWS-related behavior disorders.
- *Sexual behavior:* Normalization of physical function and appearance increases the likelihood of social interactions that may result in sexual activity and relationships. Age-appropriate counseling, caretaker education, birth control precautions, and minimization of risks for sexual abuse and sexually transmitted disease are important elements of a comprehensive team approach.

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# Part III

## Multidisciplinary Management

*Editors' note:* The behavioral characteristics, special educational and developmental needs, and lifelong support issues of those with Prader-Willi syndrome appear to be universal and relatively independent of cultural influence. However, the health, welfare, and educational systems that provide needed services vary widely from country to country as a function of the cultural and financial resources supporting those systems. Because the authors of this section are all from the United States, these chapters primarily reflect the U.S. cultural and economic framework for provision of these services. For example, the chapters on speech and motor development refer parents seeking services such as speech therapy and physical or occupational therapy to state-operated early intervention programs. Those in countries with a national health system that provides these services as needed may find the need to specially seek and qualify for these services quite foreign. Additionally, the educational sections are written within the framework of the U.S. system for those with "special educational needs." This education system, although mandated by federal law, is nonetheless both funded and administered by each individual state. Differential interpretation and funding of these federal mandates among states, between local educational units and the state, and between parents and local educational units can be an enormous source of stress for parents seeking an optimal educational experience for their youngster. Finally, there are differences by state in the provision of adult care services such as supported living.

We ask forbearance from those readers whose country's health, social welfare, and educational systems are significantly different from those in the United States. Nevertheless, we hope that the experience and wisdom offered in the following chapters will be helpful to all in managing some of the issues with which we have struggled in serving people with Prader-Willi syndrome.



# Neurodevelopmental and Neuropsychological Aspects of Prader-Willi Syndrome

Barbara Y. Whitman and Travis Thompson

Almost 50 years after originally described, Prader-Willi syndrome (PWS) continues to unfold, revealing complex physiologic, genetic, and behavioral mechanisms that often seem contradictory to standard medical and clinical understandings. This is particularly true regarding the accompanying neurodevelopmental/behavioral complex (sometimes termed behavior phenotype). While still primarily noted for the distinctive food-related behavioral constellation, PWS is characterized by a far broader neurodevelopmental profile including a distinctive cluster of behavioral features along with mental retardation or learning difficulties. Even so, this profile is neither universal nor uniform; considerable phenotypic variability is observed among affected individuals and in the same individual over time.

Understanding this phenotypic variability is further complicated by several published series that report varying rates of major behavior features. Some of this reported variability is reflected in studies that either predate, or postdate, both consensus diagnostic criteria (1993)<sup>61</sup> and comprehensive confirmatory genetic technology (mid to late 1990s, M.G. Butler, personal communication). Thus, part of the reported differences may result from different ascertainment and diagnostic strategies.<sup>8,25,55</sup> Further, previously unaccounted for genetic variation (chromosome 15 deletion versus uniparental disomy [UPD]) may be the source of additional variability.

Recent studies suggest that only hyperphagia, skin picking, stubbornness, and temper tantrums are common to most affected individuals,<sup>43</sup> yet substantial variation is observed even among these common characteristics. A clear understanding of the genetically driven neurobehavioral profile and the impact of environmental influences on the expression of this behavioral profile is pivotal to addressing issues of intervention and remediation, yet our understanding of these aspects of the syndrome remains rudimentary and imperfect—a state of affairs that frustrates parents and caregivers alike.

In this chapter we will summarize the current understandings of the neurodevelopmental/behavioral aspects of PWS. It is first necessary, however, to discuss several historical and methodological factors that

influence the status of research in this area. These include diagnostic/genetic issues, an underappreciation of the pervasiveness of central nervous system involvement, inadequate cognitive and behavior measurement tools, and a strong bias toward measuring problematic behaviors.

## **Factors Influencing Current State of Research**

### **Diagnostic/Genetic Issues**

It is only in the last decade that consensus diagnostic criteria and confirmatory genetic testing for PWS have been readily available. For those with a deletion, genetically confirmed early diagnosis became possible in the early 1980s when high resolution chromosome techniques became available in most cytogenetic laboratories. These techniques, however, required experience to avoid false positive and false negative reporting. Further, these techniques were insensitive to those with uniparental disomy.

Full, reliable and valid laboratory confirmation was not certain until methylation PCR became readily available to most genetic testing laboratories in the mid to late 1990s (M.G. Butler, personal communication, 2003). Prior to that, diagnosis was often suspected but delayed until the emergence of the abnormal eating constellation and obesity. For those with a deletion, the average age at diagnosis was 6 years, and for those with uniparental disomy, age 9.<sup>12</sup> Even today, a small but significant number of youngsters appear to meet the majority of diagnostic criteria and match the behavioral profile for Prader-Willi syndrome yet fail diagnostic confirmation by genetic testing. Earlier study populations that had neither the benefit of standardized criteria nor genetic confirmation likely included some persons who did not have PWS; the influence of these individuals on the data is indeterminable at this point. Further, even among those with PWS, study participation may have been biased toward those with the most intense or severe behaviors.

Thus while behavior studies prior to the early 1990s can be helpful, later studies of behavior that include only those with genetic confirmation of PWS must be given greater weight. Further, since robust and reliable categorization of genetic subtype (deletion, uniparental disomy [UPD], or imprinting center defect) is even more recent, studies of the differential impact of genetic subtype on behavioral outcomes are in their infancy.

### **Underappreciation of the Pervasiveness of Central Nervous System Involvement**

Because of the constellation of metabolic abnormalities associated with PWS, the (hypothesized) central etiologic role of hypothalamic dysfunction is frequently emphasized, often to the exclusion of other brain mechanisms. Yet the typical pattern of cognitive and learning deficits associated with PWS makes it clear that PWS is a pervasive (affecting

many areas of the brain) neurodevelopmental disorder. Affected individuals evidence a wide range of cognitive (dis)abilities, often with an overlay of emotional symptoms (depression, anger dyscontrol) that derive, in part, from interactions with particular environments. Four separate sources of cognitive deficits have been identified: (1) depressed general cognitive functioning or IQ,<sup>73</sup> (2) general processing deficits including short-term memory,<sup>90</sup> (3) language processing deficits,<sup>7,69</sup> and (4) an inability to meld diverse and detailed internal information into relevant higher-order abstract and metacognitive concepts that guide behavior over the long term.<sup>82,93</sup> Each of these deficits implies the involvement of multiple neural systems, far beyond that predicted from hypothalamic dysfunction alone. Additionally, affected individuals display an evolving, multistage behavioral picture that differs somewhat between those with a deletion and those with uniparental disomy. Again, hypothalamic dysfunction alone renders an insufficient accounting of the observed complexities. Clearly the neurodevelopmental/neurocognitive picture associated with PWS reflects the dysfunction of a distributed brain system, the complexities of which have yet to be described either anatomically or neurophysiologically.

### **Inadequate Cognitive and Behavior Measurement Tools**

Tools that measure cognition and behavior are frequently imprecise and focus on only a small segment of behavior. For instance, many IQ tests fail both to detect and to account for speech and language deficits. And while speech and language deficits can be separately tested, the interplay between speech and language deficits and uneven cognitive abilities is more difficult to demonstrate. Additionally, many earlier studies failed to use standardized behavioral measures, or used measures standardized on cognitively normal populations. The uncritical application of measures standardized in normal or non-PWS populations may inaccurately describe and overestimate the severity of behaviors noted in affected individuals. Further, some researchers measure the occurrence of specific behaviors<sup>44,45</sup>; others use measures that summarize several behaviors into more abstract conceptual groupings (e.g., the internalizing/externalizing factors of the Child Behavior Scale by Achenbach<sup>25,38</sup>) and personality traits (e.g., California Child Q Set<sup>24,86</sup>), the relevance of which for a PWS population has yet to be established.

An additional measurement problem is found in a number of studies. Both children and adults with PWS can be particularly difficult to test. Shortened attention spans and reduced tolerance for things that are difficult for the individual, combined with expressive language difficulties and, for many, slower-than-average processing speeds, frequently lead to behavioral refusals to complete testing protocols. As a result, many studies that use IQ scores as an independent variable rely on reports from previously administered tests for which the reliability, validity, and margin of error surrounding test administration cannot be established. Therefore results from studies using this methodology for determining IQ must be considered tentative.

### **A Bias Toward Measuring Problematic Behaviors**

From the earliest efforts, behavioral studies have been primarily focused on describing and quantifying the development and severity of problematic behaviors and emotional/psychiatric disorders associated with PWS to the exclusion of behavioral strengths. Despite a clear call by Dykens et al.<sup>38</sup> in 1992 to include investigations of strengths and adaptive behaviors, this remains a rare focus in subsequent studies. Moreover, many studies include an age range encompassing infants through middle adulthood measured at a single point in time. Such a methodology makes it difficult to understand age-related behavioral issues. Further, depending on the nature of the investigation, the use of a comparison group may be appropriate, but defining an appropriate comparison group presents additional difficulties.<sup>34</sup> Newer brain imaging and neurophysiologic techniques offer an avenue for developing a more complete understanding of the neurobiologic substrate of behavior, but these techniques can be particularly difficult to use with this population.

Despite these difficulties, studies across time, taken together, provide a broad, general picture of behavior in PWS. Let us look at the various components of this complex behavior as we currently understand them.

### **Food-Related Behaviors**

As indicated, the neurobehavioral picture associated with Prader-Willi syndrome is far broader than the food-related behavior constellation. Nonetheless, this constellation remains the primary defining feature of the syndrome for most family, health, and other care providers. And, when poorly or improperly managed, hyperphagia along with the resulting obesity and the associated negative behavior usually are the central difficulties for which families seek help. However, hyperphagia is only one of many behaviors in the food-related behavioral constellation, which also includes preoccupations surrounding food; food-seeking/foraging; sneaking, hiding, and hoarding; eating unusual food-related items (sticks of butter, used cooking grease, dog food, decaying or rotten food, food-flavored items such as shampoos, etc.); and for many, manipulative and occasionally illegal behaviors in an effort to obtain food.

Hyperphagia is not unique to PWS; several syndromes and conditions include some degree of hyperphagia (e.g., fragile X syndrome, Kleine-Levin syndrome, and "normal" obesity). Nonetheless clear differences distinguish the eating patterns associated with PWS from those of other conditions. Foremost among these is the age-related emergence, rapid escalation, and intensification of hyperphagia following several years of normal to poor eating and often failure-to-thrive.<sup>30</sup> Further distinguishing characteristics include duration of eating, amount of food eaten, and a delayed to absent deceleration of eating when satiety should be apparent. Further, the hyperphagia remains refractory to even the most recent anorexigenic medications.

Several studies have compared the duration of eating of those with PWS with that of control subjects (either obese or non-syndromic origin, normal weight, or other genetically disordered individuals).<sup>48,57,100</sup> Common to all studies was full access to food by all subjects for a full hour. And in all studies those with PWS, except for the very youngest participants, continued to eat throughout the hour, while control subjects stopped eating within 15 to 20 minutes. For most nonaffected individuals, a deceleration of eating is observed prior to complete eating cessation. Many with PWS showed a slight tendency toward longer pauses between bites near the end of the study hour, however there was no indication that those with PWS would have totally ceased eating had food continued to be made available.

Noting the tendency toward slightly longer pauses near the end of the study hour, several follow-up studies used a similar methodology with the exception that when the participants with PWS appeared to be finished, they were asked to leave the room.<sup>2,70</sup> With this slight modification, all participants with PWS finished eating in 45 minutes. This was still substantially longer than control subjects, who, as before, completed eating in 15 to 20 minutes. In addition to an extended duration of eating compared with control participants, those with Prader-Willi syndrome consumed far greater quantities of food than nonaffected controls. Several authors reported that even when those with PWS appeared satiated and stopped eating, the satiety was short-lived and food seeking resumed far more rapidly than in an unaffected population.<sup>57</sup>

The failure of appetite control is also reflected in studies designed to look at food choices of persons with Prader-Willi syndrome, particularly those that look at a choice between a larger quantity of food versus a smaller quantity but more desirable food.<sup>13,31,85</sup> A recent study offered a choice between immediate access to a small amount of a previously determined favorite food of the participant versus a larger amount of a less-preferred food following a brief time delay.<sup>64</sup> Seven persons with PWS and six matched obese persons participated. In all instances, those with PWS opted for the delay followed by the larger quantity, while the control group was equally likely to select the smaller amount of more-desired food as to delay for quantity. A similarly designed, larger follow-up study offered an immediate but small amount of a desired food versus a delay followed by a larger amount of the same food. Similar results were obtained.

That food seeking is prevalent among those with PWS is not surprising, given these results, and indeed at least 50% of those affected actively seek food<sup>31</sup> including foraging for food and food stealing.<sup>5,62</sup> Food seeking typically occurs covertly. Clinical data and anecdotal reports are rife with stories of food-seeking incidents by affected individuals and the impact of these behaviors on obesity management, family stress, and the ultimate adjustment of both the affected individual and his/her family.<sup>1,17,43</sup> For some, food seeking is opportunistic; that is, if food is accessible and usual caretakers are absent or otherwise preoccupied (e.g., parent talking with a friend), the affected individual seizes the opportunity, often hiding the prize (usually in clothes) for

later consumption. Others are more active in *making* opportunities, such as “borrowing” money from a parent’s wallet for later food purchase, or asking to use the school restroom and while en route “checking out the desk” of a teacher known to keep candy in a desk drawer. At the most severe end, many look for every opportunity to escape the confines of a caregiver so they can seek food, be it from neighbors, local groceries, or any other source of abundant food.

In addition to extraordinary food-seeking and eating behaviors, even ordinary conversation reflects a constant preoccupation with food. Clinical descriptions indicate a constant need to know when the next food will be available, what that food might be, how much will be served, how it will be cooked, and an assurance that the information provided is certain. In the larger environment, food or restaurant advertisements, newspaper and magazine pictures and recipes, and other visual reminders of food frequently become the subject of discussion and “collections.” And jigsaw puzzles, a favorite pastime of many persons with PWS, become even more enjoyable when the subject of the puzzle is food related.

### **Etiology of the Abnormal Food-Related Constellation**

The etiology of hyperphagia in PWS has long been attributed to a hypothalamically mediated failure of satiety control,<sup>21,57,70</sup> a view at least partially supported by post-mortem documentation of specific hypothalamic abnormalities.<sup>81</sup> However, other emerging possibilities suggest a far more complex etiology than previously considered,<sup>11,56</sup> including a complete theoretical reorientation that views PWS as a *starvation syndrome* rather than an obesity syndrome. In this view, the obesity of PWS is seen as resulting from a physiologic signaling defect indicating that the body is in a constant state of starvation, similar to that of malnourished youngsters.<sup>59,68</sup> While the implications of this reorientation compared with the view of PWS as an obesity syndrome are beyond the scope of this chapter, such a possibility suggests a basis for explaining the failure of the food-related behaviors to respond to anorexigenic or obesity medications.

In the absence of adjunctive medications, treatment remains primarily behavioral and preventive. Strategies for preventing and coping with this behavior vary according to individual characteristics and family needs.<sup>52</sup> A more complete discussion of these strategies is found elsewhere in this volume (see Chapters 12 and 18).

## **Cognitive Characteristics**

### **Level of Intellectual Functioning**

Decreased intellectual functioning, presumably in the form of mental retardation, was among the four original defining characteristics of PWS.<sup>32,71,99</sup> Those studies<sup>12,22,33,39,55,63,99</sup> in which individual test results or ranges have been reported document a wide range of intellectual abilities, with overall IQ scores ranging from 12 to 100. Curfs’s and Fryns’s<sup>23</sup>



oft-quoted summary of 57 studies including 575 individuals of unspecified ages from a number of countries yielded the following distribution of IQ scores: Normal 4.9%, Borderline 27.8%, Mild Mental Retardation 34.4%, Moderate Mental Retardation 27.3%, Severe to Profound Retardation 5.6%. However, methodologic concerns render these figures questionable. First, the included studies varied from case reports to large surveys. Few of the study populations were genetically confirmed, raising the likelihood that the studies included those who did not have PWS. Further, few authors reported the basis for determining mental retardation, a fairly important issue for the time period, considering IQ thresholds for mental retardation were substantially higher than present criteria. (Prior to 1973, Full Scale IQ scores of less than 85 were considered in the mental retardation range. A 1973 revision of criteria lowered thresholds for mental retardation to Full Scale IQ scores of less than 70.) Further, many studies failed to include measures of adaptive behavior, relying solely on IQ scores to determine the presence of mental retardation, thus failing dual criteria requirements.

In addition to uncertainties regarding the criteria for determining the level of cognitive functioning, there are equally important methodological concerns regarding IQ measurement and the validity of the scores included in the Curfs and Fryns survey.<sup>23</sup> Recall that these percentages within IQ ranges were calculated by averaging across a number of studies. Both the instruments used and the testing methods varied widely across studies. Studies that use a broader range IQ test (e.g., the Wechsler series) obtain different IQ results than those using a more narrowly focused, verbally based instrument (e.g., earlier versions of the Stanford-Binet) that emphasizes verbal abilities more heavily than non-verbal abilities. Secondly, there was no standardization across testing methods nor among those administering the tests. Thus some studies administered all the required subtests while others administered a subset and prorated overall scores from that subset. In addition, some studies required completion of all test protocols at a single sitting, while others spread the testing over several days in order to minimize interference from short attention spans and fatigue. Thus, differences in scores may reflect differences in tests and administration rather than real differences in intellectual abilities. Further, there was a wide age range included in the studies. For example, in a study including those from age 4 years to age 44 years, reported IQ scores may include many who are age 4 and whose test results indicate IQ scores obtained at age 4. This same study may also include three persons who are age 20. However, the included IQ scores were measured at different ages for each individual, such as age 12 for one, 16 for another, and 20 for the third. Finally, there is no accounting for the impact of educational differences on IQ scores among the studies.

A valid determination of cognitive ranges requires: (1) genetic confirmation of the diagnosis; (2) directly and validly administered, age-appropriate standardized testing; and (3) measures of adaptive behavior. While several recent studies included genetic confirmation of the study population, few included direct IQ assessment and determination of adaptive status, depending instead on previous school-based

or developmental clinic testing.<sup>43</sup> Others utilized prorated scores from selected subtests or combinations of these methods.<sup>1,39,50,78</sup> Five recent studies meet the majority of these criteria. They are summarized in Table 8.1. The Israeli data<sup>54</sup> are remarkable for the large percentage of children testing in the normal range. The authors reported that this sample of 18 represents 86% of the total number of individuals with Prader-Willi syndrome known in Israel. Clearly this population has a distribution of IQ scores that is quite different from the remaining four studies, so it will be considered separately. Averaging across the four remaining studies, all with approximately the same number of participants, 25.5 % have IQ scores above 70, 43% score in the range of Mild Mental Retardation, 27.7% in the region of Moderate Mental Retardation, and 3.8% in the Severe to Profound range. When compared with Curfs's and Fryns's 1992 estimates,<sup>23</sup> this combined sample of 203 subjects yields substantially fewer who score in the Borderline to Normal range (32.7% versus 25.5%) and a substantially greater portion scoring in the category of Mild Mental Retardation (see Table 8.2). Recall, however, that these are cognitive scores only. Although most authors administered an adaptive behavior measure, most did not report these scores. If we assume that many with IQ scores in the 70–75 range would be reclassified as mildly mentally retarded on the basis of their adaptive behavior profiles, then these figures are only approximate, with the true percentages in the borderline range expected to be

Table 8.1. Recent Studies of IQ in Individuals with Prader-Willi Syndrome

| Study                              | N  | Avg Age           | Percent of Subjects Testing in Each IQ Range |            |         |         |                  |
|------------------------------------|----|-------------------|----------------------------------------------|------------|---------|---------|------------------|
|                                    |    |                   | Normal                                       | Borderline | Mild MR | Mod. MR | Severe/ Profound |
| Einfeld et al. <sup>43</sup>       | 46 | 17.7 <sup>a</sup> |                                              | 21.6*      | 64.9    | 13.5    | 0.0              |
| Gross-Tsur et al. <sup>54</sup>    | 18 | 14.3 <sup>b</sup> | 17.0                                         | (73.0)*    | 56.0    | 27.0    | 0.0              |
| Descheemaeker et al. <sup>28</sup> | 55 | 14.1 <sup>c</sup> | 9.0                                          | (25.4)*    | 16.4    | 27.3    | 40.0             |
| Whittington et al. <sup>98</sup>   | 55 | 21.0 <sup>d</sup> | 5.5                                          | (31.0)*    | 25.5    | 41.8    | 27.2             |
|                                    |    |                   | IQ ≥ 70                                      |            | 60–69   | 50–59   | ≤49              |
| Roof et al. <sup>72</sup>          | 47 | 23.2 <sup>e</sup> |                                              | 24.0*      | 38.0    | 30.0    | 8.0              |

\* Subjects testing at Normal or Borderline; the numbers in parentheses are sums of the Normal and Borderline subjects in those studies, provided for comparison purposes with the Einfeld et al. and Roof et al. data.

<sup>a</sup> Age range: NA. Only half of subjects genetically confirmed; most IQs from records. (S.L. Einfeld, personal communication, 2004)

<sup>b</sup> Age range: 8.3–23.5yrs. Did not give a measure of adaptive functioning.

<sup>c</sup> Age range: 1–49 yrs. (A. Vogels, personal communication, 2004)

<sup>d</sup> Age range: 5–46 yrs.

<sup>e</sup> Age range: 10–55 yrs.

**Table 8.2. Estimates of IQ in Prader-Willi Syndrome Based on Multiple Studies**

| Survey                         | N   | Percent of Subjects Testing in Each Range |            |         |         |                 |
|--------------------------------|-----|-------------------------------------------|------------|---------|---------|-----------------|
|                                |     | Normal                                    | Borderline | Mild MR | Mod. MR | Severe/Profound |
| Curfs and Fryns <sup>23a</sup> | 575 |                                           | 32.7       | 34.4    | 27.3    | 5.6             |
| Author <sup>b</sup>            | 203 |                                           | 25.5       | 43.0    | 27.7    | 3.8             |

<sup>a</sup> Summary of 57 studies; subjects' ages unspecified.

<sup>b</sup> Averages of data from four recent studies shown in Table 8.1, excluding data from Gross-Tsur et al.<sup>54</sup>

somewhat lower while those in the mild mentally retarded range would be somewhat higher.

At least one group of authors<sup>98</sup> suggests that (with the exception of the Israeli group) the distribution of scores approximates the normal curve usually associated with IQ scores, but with a mean shifted downward 30–40 points. They attribute this to a “direct and specific effect on brain development because of the absence of expression of an imprinted gene that is part of the PWS genotype.”<sup>98</sup> This explanation, however, cannot account for the very different distribution underlying the Israeli data. To the extent that the Israeli scores reflect real differences in cognitive functioning, the source of these differences must be investigated.

### Stability of Cognitive Functioning

In addition to the levels of cognitive ability, several additional aspects of cognitive functioning have been investigated. Early cross-sectional reports suggested that IQ scores in PWS decline with age<sup>22,32,76</sup> Subsequent studies failed to support a decline in IQ scores over time,<sup>39,53</sup> leading to the conclusion that, in contrast to other genetic disorders (e.g., fragile X and Down syndromes) the cognitive trajectories of those with PWS appear to be stable over time. However, the issue is again raised when examining the Israeli and Belgian data (data provided by A. Vogels; personal communication, 2004). In the Israeli data, significant age-related differences are apparent among those with a deletion. Subjects 12 years and under had significantly higher Full Scale IQ scores (78 versus 67,  $p < 0.10$ ) and Verbal IQ Scores (86 versus 66,  $p < 0.05$ ) than those over 12. No age-related differences were found in Performance IQ or Child Behavior Checklist Scores. The UPD sample size was insufficient to examine this issue. Similarly, dividing the Belgian data into those over (IQ = 57.2) and under age 12 (IQ = 63.8), a trend toward a significant reduction ( $p = 0.09$ ) in IQ scores is noted for the older group. The English data (J.E. Whittington, personal communication, 2004), however, do not follow this trend. Full clarification of this issue requires longitudinal studies of several cohorts of affected individuals.

### Academic Underachievement

It is generally accepted that across the cognitive spectrum, academic performance is substantially below that predicted by overall IQ scores, although exceptions are noted.<sup>9,39,72,90,97</sup> Part of this discrepancy may be a computational artifact associated with the calculation of Full Scale, Verbal, and Performance IQ. When test protocols are closely examined, most affected individuals demonstrate wide individual variability among the subtest scores comprising an overall IQ (subtest scatter). This uneven pattern of cognitive abilities is similar to that seen in children with learning disabilities.<sup>26,54</sup> When significant subtest variability exists, overall IQ scores are an unreliable and frequently inaccurate predictor of cognitive abilities, even among a population unaffected with PWS.

The remainder of the discrepancy is most likely attributable to specific areas of learning disability as indicated by the subtest scatter. The three areas most impacted are variously cited as reading, spelling, and arithmetic. The impact of these learning disabilities on academic underachievement varies by academic domain and by genetic subgroup. Roof et al.<sup>72</sup> compared the intellectual features and academic achievement of 24 persons with a deletion subtype and 14 persons with UPD. On average, those with UPD had significantly higher Verbal IQ scores than those with a deletion. Additionally, Verbal IQ scores exceeded Performance IQ scores for those with UPD, while those with a deletion evidenced the opposite pattern. When Verbal and Performance scores are averaged to yield an overall IQ, the IQ scores are not significantly different between the two groups. Thus, it appears that those with UPD may have relatively greater verbal skills, while those with a deletion evidence relatively greater visual-perceptual-spatial abilities. Since each of these relative strengths would have a differential impact on academic outcomes, there was no overall difference in performance between the subtypes. By contrast, two recent studies found that, on average, those with a deletion do substantially poorer on reading and spelling than do those with UPD (many of whom reach expected achievement levels in these two areas). There is little difference between the two groups on math skills, which are uniformly depressed.<sup>9,97</sup> In addition, among those with a deletion, the size of the deletion differentially impacts academic outcomes. Those with a type I deletion lose an additional 500 kb of genetic material in addition to what is missing in type II deletions.<sup>9</sup> Measures of academic achievement are strikingly poorer for those with a type I deletion than for those with a type II. To the extent that these differences exist, they may further reflect differences in brain development due to varying amounts of material on the paternally contributed member of the chromosome 15 pair.

### Specific Deficits in Learning, Memory, and Cognitive Processing

A number of investigators have examined the relationship between intellectual deficits, academic underachievement, and specific cognitive processing deficits. Findings suggest deficits in visual and auditory

attention and short-term memory, whereas long-term memory appears less impaired.

There are few studies on learning and memory in PWS. Warren and Hunt<sup>90</sup> found children with PWS performed less well on a picture recognition task than children with mental retardation of unknown etiology matched for chronological age and IQ. The two groups of children performed similarly on a task meant to measure access to long-term memory. The authors concluded children with PWS have a deficit in short-term visual memory, but not in long-term visual storage. The authors also compared cognitive capabilities of adults with PWS and controls matched on mental age and IQ. PWS participants with difficulty in short-term memory processing lost more information that was learned over time compared with controls. A recent study by Stauder et al.<sup>75</sup> extends these earlier findings, documenting that the auditory modality in PWS is even more affected than the visual and that short-term memory is impaired. As with other areas of cognitive processing, genetic subtype exerts an influence. The recent work of Joseph et al.<sup>65</sup> found that visual memory is a specific strength among individuals with maternal disomy. Specifically, she found that the rate of short-term memory decay among individuals with maternal disomy was considerably slower than that of either PWS individuals with deletions or matched controls.

Visual perception, organization, and puzzle-solving skills have been reported as relative strengths in some people with PWS. Taylor and Caldwell<sup>84</sup> reported Wechsler Adult Intelligence Scale (WAIS) subscores for adults with PWS and obese control participants matched for overall IQ. The highest subtest scores for the participants with PWS were on picture completion, object assembly, and block design. Similarly, block design on the Wechsler Intelligence Scale for Children (WISC) emerged as a strength for 9 of 26 children with PWS,<sup>26</sup> suggesting that some individuals with PWS have the ability to recognize and evaluate figural relations greater than would be expected based on other aspects of cognitive functioning.

To the extent that there are fundamental visual processing differences between genetic subtypes, these differences would be reflected in more basic cognitive-perceptual processes. Fox et al.<sup>49</sup> looked at subtype differences in the discrimination of familiar shapes (square, rectangle) generated through the motion of random elements. While not in normal ranges, the deletion group performed as well as others with non-specific intellectual disability, but the UPD group was significantly worse. However, in a follow-up study using photographs of familiar non-food *and* food-related objects, the UPD group demonstrated better short-term visual memory than the deletion group. Thus the question of subtype differences in basic cognitive processes and intellectual abilities remains open.

Additional cognitive processing differences are suggested in the work by Dykens et al.<sup>39</sup> Using the Kaufman Assessment Battery for children, the authors report significant sequential processing deficits with relatively stronger simultaneous processing abilities in a group of adults with PWS of mixed genetic origin. This must be considered a

tentative finding as the population tested was outside the age ranges for which the test was standardized and normed. Reports of superior puzzle-solving ability in PWS individuals would be consistent with this hypothesis.<sup>35,60</sup> Additional studies of the basic cognitive processes (visual and auditory perception, visual and auditory processing, and memory) and learning styles are critical for designing more effective educational and behavioral programs.

### **Language Processing Deficits**

The speech and language characteristics of those with PWS are dealt with at length elsewhere in this volume (see Chapter 9). This section provides a brief summary of these findings as one aspect of the neurodevelopmental and neurocognitive components of PWS. A number of authors document delays in spoken language development (e.g., Kleppe<sup>66</sup>). While these delays may, in part, reflect poor muscle tone and reduced breathing capacity leading to reduced oral motor skills, it also appears that deficits in understanding and using language impact both spoken and written language. Language development typically follows a progression from hearing and understanding (receptive language) to speaking (expressive language) single words, two-word phrases, two-word sentences, and eventually interactive conversation. A number of speech-related difficulties have been found: (1) both delays and deficiencies in receptive language including difficulty with auditory discrimination (later, phonics or sounding out words is usually impaired), (2) vocabulary deficits, (3) sub-optimal understanding of sentences,<sup>82</sup> (4) limited ability to talk in sentences, and (5) poor understanding and use of language in a communicative context (pragmatic skills).

### **Higher-Order Processing Deficits**

While a number of authors allude to higher-order processing deficits, little direct research has been done in this area. However, indirect evidence strongly indicates marked difficulties in this area. Higher-order cognitive processing encompasses such abilities as abstract thinking, executive functions, and metacognitive abilities. A number of authors describe the concrete thinking style associated with PWS across cognitive capacities. Thus, many affected individuals will show an inability to change perspectives even when proven wrong<sup>79,82</sup> and an inability to generalize from one situation to another or to see the commonalities across situations. In addition, many affected individuals are co-morbid for Attention-Deficit Disorder (ADD), demonstrating both attentional deficits and impulsivity in multiple settings.<sup>54,95</sup> Metacognitive abilities are defined as "thinking about thinking" or the use of executive processes in overseeing and regulating cognitive processes. Both the concreteness and rigidity of thinking, combined with attentional deficits and the judgment failures of impulsivity give evidence to a marked lack of metacognitive processes. Thus, both academic and social functioning are impacted by an inability to mobilize executive functions and use memory, visuomotor skills, language, and judgment in concert to solve multifaceted problems.



## Behavior and Personality

Not illogically, both early and recent work in this area has been heavily focused on understanding the developmental trajectory, range, and severity of problem behaviors frequently associated with PWS. There has been relatively less focus on the positive behavior characteristics and personality strengths. In part this seemingly skewed focus reflects a continuing critical need for effective intervention programs. It may also reflect a real characteristic of the behavioral picture associated with PWS, i.e., a tendency toward a “negative” personality profile with a preponderance of difficult behaviors. Multiple studies using multiple behavior measures clearly document that, separate from the food-related behavioral difficulties, affected individuals are more prone to behavioral disturbances including age-inappropriate temper tantrums, stubbornness, skin picking, impulsivity, and ritualistic and repetitive behaviors<sup>14,18,38,41,55,80,95</sup>. Further, the overall rate, severity, and chronicity of these disturbances are frequently more intense than those associated with comparable genetic or cognitive impairments<sup>17,25,40</sup> or other obese groups.<sup>1</sup> However, this difficult behavior picture is largely absent for the first few years of life. Indeed, most authors agree that, on the whole, infants and young toddlers with PWS are affectionate, placid, generally cheerful, largely compliant, and usually cooperative. Further, most authors agree that as the hyperphagia emerges, a separate and distinctly negative behavioral shift is also observed.<sup>4</sup> Unfortunately, the historic reliance on hyperphagia for diagnostic confirmation delayed systematic observation of these early behavioral characteristics until genetic technology supported early diagnosis. Thus, until recently, there was little available data regarding the behavioral and emotional characteristics of the first 2 years of life beyond that found in routine medical records. Therefore the question to be posed is: Is this shift simply a normal developmental process (i.e., the “terrible twos”), or is this an age-related expression of Prader-Willi syndrome—or both?

### Behavior Development Across Time

At least three recent studies have looked at the nature of behavior changes in toddlers with PWS.<sup>1,29</sup> Akefeldt and Gillberg<sup>1</sup> examined three groups of affected individuals seeking to determine (1) which behavior and personality characteristics in PWS are primarily linked to the syndrome and not to cognitive levels or weight and (2) if behavior problems are age-related. The youngest group ranged in age from 8 months to 43 months; a second group ranged from 7 to 36 years of age and had received no medication treatment of any sort (either psychotropics or growth hormone); while a third group ranged in age from 4 years 2 months to 36 years 3 months and had received some kind of medication treatment. An age- and BMI-matched comparison group, approximately half of whom were also mentally retarded, served as controls. Behavior was measured with (1) the Swedish translation of the Rutter scales, a parent report instrument of behavior problems in the home setting; (2) the Asperger and High Functioning Autism

Screening Questionnaire; and (3) the Eating Attitudes Test. All but the youngest group were also administered the Birleson Depression Questionnaire. In addition, the youngest group had a mean Rutter score of 2.8 while the two older groups had mean scores of 11.6 and 12.8, respectively. Within the youngest group, parents reported an accelerating interest in food and an increased need for routine beginning around age 2 and a subsequent increased tendency toward stubbornness emerging around age 3. While some of these changes may reflect normal developmental processes (e.g., the "terrible twos"), unlike typically developing youngsters, the data indicate that those with PWS evidence no remission from this stage. Instead the data point to an evolving, increasingly difficult behavioral picture that intensifies with age.

Individuals with PWS aged 7 years and older showed a specific behavior pattern and characteristic personality traits that clearly differentiated these youngsters from the controls. These were skin picking; fussy, overly particular behavior; insistence on certain routines; aggressive behavior; very changeable mood; and preoccupation with food. Many of these behaviors were already present in those younger than age 5. A similar study of 58 individuals aged 3 to 29 years yielded essentially the same findings.<sup>77</sup>

Dimitropoulos et al.<sup>29</sup> sampled 105 children ranging in age from 2 to 6 years. These children were compared with an age-matched group of children with Down syndrome and a separate age-matched group of typically developing children. All groups were compared on the Early Child Developmental (age 2) or the Preschool Child Developmental (age 3) Inventories, a tantrum behavior survey, and a Compulsive Behavior Checklist for Clients with Mental Retardation. The children with PWS were clearly distinguished from both the youngsters with Down syndrome and the typically developing children. All groups demonstrated an emergence and escalation of both food-related and other tantrums; a shorter tolerance for frustration combined with an overreaction to frustration; repetitive and ritualistic behavior; and other behavior problems including increasing oppositional tendencies, a lessened ability to "go with the flow," and increasing stubbornness and "rigidity." However, the two comparison groups exhibited such behaviors *only transiently*; that is, the problems appeared and then subsided. The development of such behaviors in those with PWS was not transient, instead seeming to escalate with increasing age. Additionally, the onset of these behaviors in the PWS group was independent of intellectual, language, and motor abilities. For some with PWS, skin picking was already beginning to emerge. Taken together, these studies strongly indicate that the early emergence of unremitting negative behaviors is more likely a syndrome-driven phenomenon rather than an age-related, normal developmental process. However, since these scores are cross-sectional rather than longitudinal (i.e., following the same group over time), further investigation is warranted.

Other authors have also looked at the second shift that was previously indicated as occurring somewhere around 7 to 8 years of age. These changes include an escalation of the earlier-described behavioral

pattern along with a significantly increased rigidity of behavior,<sup>1,24</sup> including the tendency to “get stuck” on a thought or question; increasing concerns for real and imagined worries; less responsiveness to caregivers’ efforts to elicit flexibility, to redirection, or to “calming down until reasonable” alternatives; a tendency to “fly off the handle”; and a clear falling behind age-matched peers in social skills. At this age point, both skin picking and daytime sleepiness stand out as major behaviors that distinguish this group of children with PWS both from younger children with the syndrome and from other age-matched children with mental retardation. At the level of personality traits, parents of children with PWS report their children as less agreeable, having lower emotional stability and openness, and showing increased irritability compared with age-matched, typically developing peers.<sup>86</sup>

Emotional lability; temper tantrums; skin picking; repetitive, ritualistic, and compulsivelike behaviors; and hoarding become particularly prevalent in adolescents with PWS, distinguishing this age group from both younger children and older individuals with PWS, as well as from typical adolescents.<sup>14,38,55,91</sup> Furthermore, these difficulties persist into early adulthood.<sup>25,43,53,95</sup> Although some behavior modulation is often seen in later ages, nonetheless problematic behaviors still exceed those seen in other comparison groups.<sup>17,43</sup>

Unlike many other genetic syndromes, the behavior differences among those with PWS appear to be largely independent of gender, cognitive level, or weight, although an occasional study has reported a sex- or weight-specific finding.<sup>24,36,95</sup> By contrast, *genetic subtype* may differentially influence the behavioral picture. An early study by Wenger et al.<sup>92</sup> indicated no difference between those with a deletion and those without; however this study was conducted prior to routine genetic confirmation, particularly of those with uniparental disomy, and may have included individuals who did not have PWS. Dykens et al.<sup>37</sup> compared the problematic behavior of 23 genetically confirmed individuals with a deletion and that of 23 age- and gender-matched PWS persons with genetically confirmed UPD. Their findings suggested that, compared with those with UPD, individuals with a deletion had both a greater quantity of and more severe problematic behaviors. Specifically, those with a deletion had more problematic eating behaviors, were more underactive, were more withdrawn, sulked more, more often skin-picked and bit their nails, and engaged in more hoarding behavior. Those with a deletion also obtained higher severity scores on the Yale-Brown Obsessive Compulsive Scale (Y-BOCS) than did the UPD group. Butler et al.<sup>9</sup> compared 12 individuals with type I deletions to 14 individuals with type II deletions and 21 with UPD. In general, those with type I deletions had poorer behavior and psychological functioning coupled with reduced independent behaviors than those with either type II deletions or UPD. In most, but not all, instances those with a type II deletion scored midway between those with a type I deletion and those with UPD. However, studies by Gross-Tsur<sup>54</sup> and Steinhausen et al.<sup>77</sup> found no behavioral differences between the typical deletion and UPD genetic subtypes. The behavioral impact of genetic subtype appears to be extremely complex, requiring

further research to fully understand. Indeed, genetic subtype may have a greater influence on the later development of psychiatric disorders, a subject to which we will later return.

Vogels et al.<sup>89</sup> assessed the *personality* dimensions of extroversion, agreeableness, consciousness, emotional stability, and openness to experience. In general, those with PWS scored more negatively on all dimensions than age-matched controls. This was particularly true for the subdimension of benevolence. A further difference was found between those with the isodisomy form of UPD (two identical maternal chromosome 15s) and those with imprinting center defects. The children with isodisomy UPD were significantly more benevolent and conscious (or more empathic and considerate) of others than were children with imprinting center defects. This is one of the few studies to assess personality on standard personality measures.

### **Adaptive Behavior**

There has been very little formal assessment of adaptive behavior functioning in persons with PWS. Taylor<sup>83</sup> reported Adaptive Behavior Scale (ABS) data from an unpublished study conducted by Taylor and Caldwell.<sup>84</sup> 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 I of the ABS was in the physical development category, where the participants with PWS had scores that were 34% below those of the control group. Dykens et al.<sup>38</sup> attempted to establish the adaptive behavior profile of adolescents and adults using the Vineland Adaptive Behavior Scales. Daily living skills proved an adaptive strength for the group as a whole, while socialization, particularly coping skills, emerged as a relative weakness. Interestingly, the authors reported that daily living skills become more of a strength with increasing age. Similar results were reported by Holland et al.<sup>58</sup> Thompson and Butler (unpublished data) also found that PWS subjects and IQ-matched controls differed substantially in their degree of independent community living skills. The subjects with PWS appeared significantly less competent than controls. While this may indicate biologically based differences in cognitive ability, it more likely reflects the far more restricted lives led by most individuals with PWS (and therefore more limited opportunities to develop skills) due to the concerns of caregivers about access to food in uncontrolled settings.

### **Hoarding, Repeating, Ordering, Need for Sameness—Obsessive-Compulsive, Developmental Arrest, or Autistic Spectrum Disorder**

Separate from food-related behaviors and fixations, individuals with PWS exhibit other behaviors that are repetitive, ritualistic, and appear both driven and compulsive. For many, these behaviors are sufficiently problematic and disruptive that management and adjustment are negatively impacted throughout the life span. Several authors studying these behaviors assert a genetic tie between PWS and Obsessive-

Compulsive Disorder (OCD)<sup>41,74</sup> and encourage treatment with medications for obsessive-compulsive disorders.<sup>34,42</sup> Other investigators, however, view these same behaviors quite differently, remaining skeptical of a genetically based PWS-OCD link.<sup>18,58,94</sup>

Arguing that these behaviors constitute “full-blown Obsessive-Compulsive Disorder (OCD),” Dykens et al.<sup>41</sup> compared the scores of 91 older children and adults with PWS and an age- and gender-matched (cognitively normal) comparison group who had previously been diagnosed with OCD. The PWS group yielded significantly elevated scores on specific subscales of the Yale-Brown Obsessive Compulsive Scale. These included hoarding, ordering and arranging objects according to a certain set of rules, and the repetitive asking or telling subscales. The scores of the PWS group were comparable both in number and severity to the comparison group. A subsequent study by the same authors found that these characteristics were more severe and problematic in those with a deletion than in those with UPD,<sup>37</sup> leading the authors to conclude that the pathogenesis of PWS appears to predispose many individuals to obsessive-compulsive behavior, if not full-blown OCD.<sup>42</sup>

By contrast, Feurer et al.<sup>47</sup> used the Compulsive Behavior Checklist (CBC) to study 53 PWS persons with a deletion and 12 with UPD between the ages of 4 and 41 years. The CBC was designed to gather information about compulsive behaviors specifically in persons with intellectual disability. Their findings indicate that, separate from skin picking, the compulsive-type behaviors observed in those with PWS are a single behavioral dimension that is quite different in character from classic OCD, and they question the usefulness of applying such diagnostic terms to the PWS population. Common to both sets of studies was the use of volunteer subjects. It has often been found that people volunteer for studies because they have the disorder being studied, so the study population may contain a more seriously affected group than would be found in the general population. Study results that are based on such a sample may wrongly indicate an association when none exists.

In an attempt to avoid the biases associated with a volunteer study population, a recent study attempted to assess *all* persons with PWS residing in a circumscribed geographic region of the United Kingdom.<sup>18</sup> Theoretically, by sampling from the whole population, certain types of bias found in volunteer subject populations are eliminated. Ninety-three persons with PWS ranging in age from 5 to >31 years were compared with 68 intellectually impaired persons of other etiologies on the Developmental Behavior Checklist, the Aberrant Behavior Checklist, and the Vineland Adaptive Behavior Scale. The authors report a specific lack of obsessive symptoms but did observe a high prevalence of ritualistic behaviors in the PWS population. Although ritualistic, these behaviors are quite different in character from those typically described as obsessive-compulsive behaviors or those associated with classic obsessive-compulsive disorder.

Continuing to characterize the behaviors associated with PWS as a variant of obsessive-compulsive disorder is seen by many as counterproductive. Current criteria for OCD include the presence of



obsessions, compulsions, and psychological distress in the affected individual, based on the recognition that such behaviors are (1) out of the range of normal and (2) negatively impacting the affected person's ability to function. While studies clearly document repetitive, ritualistic, and compulsivelike behaviors as salient characteristics of PWS, clear evidence of classic compulsions and obsessional thinking is lacking. This latter argument is frequently countered with an argument that persons with PWS have difficulty assessing and expressing the presence of the internalizing components of obsessions. A more important argument, however, is the clear indication that persons with PWS do not view these behaviors as out of the range of normal, nor do they appear to suffer psychological distress as a result; rather, distress most frequently occurs when the person is prevented from engaging in a favored behavior. Indeed it is more often the caregiver who is bothered by these behaviors than it is the affected individual.<sup>58</sup> Recall that these behaviors appear during the same time frame and are similar in character to those found in typically developing children of the same age. Further, recall that children with PWS are distinguished from the typically developing children in that the latter develop these behaviors only transiently, while the children with PWS continue to display such behaviors. Thus, Clarke et al.<sup>18</sup> and Holland et al.<sup>58</sup> asserted that the etiology of these behaviors is a "specific pattern of atypical and arrested brain development such that the characteristic rituals and compulsions of early childhood continue and only resolve if development goes beyond that particular developmental phase."<sup>58</sup>

Yet another point of view suggests that the pattern and developmental trajectory of these behaviors is most compatible with Autistic Spectrum Disorders. Four criteria define these disorders: (1) an absence, delay, or impairments in both verbal and nonverbal language; (2) qualitative impairments in reciprocal social interaction; (3) a restricted range of interests and stereotyped patterns of behaviors and activities; and (4) a range of cognitive deficits.

At the most severe end of the spectrum are those with frank autism; however a milder variant, Asperger syndrome, has been described. Two studies directly address the presence of Autistic Spectrum Disorders in Prader-Willi syndrome. In a controlled study investigating the behavior and personality characteristics in a Swedish population of persons with PWS, Akefeldt and Gillberg<sup>1</sup> administered both verbal and nonverbal IQ tests, problematic behavior questionnaires, and the Asperger Syndrome and High Functioning Autism Screening Questionnaire to 44 persons with PWS ranging in age from 8 months to 36 years. The latter was used as a measure of social skills. Scores ranged from 0 to 54; 19 and above is considered to indicate the presence of Autistic Spectrum Disorders. The group of children aged 8 months to 3 years 8 months had a mean score of 3.4; however those whose ages were 7 years and up had a mean score of 19.1, indicating the presence of Autistic Spectrum Disorders. Since only mean scores were given, we do not know what percentage of the groups scored in the Autistic Spectrum range. Both groups scored higher on this measure than a control group.



In a study designed to look at Autistic Spectrum Disorders as the unifying framework for understanding the complex behavioral picture associated with PWS, Whitman<sup>94</sup> had parents complete the Autism Behavior Rating Scale, the Gilliam Autism Rating Scale, the Australian Asperger Scale, and the Social Skills Rating Scale, and directly assessed 18 subjects with PWS using age-appropriate IQ tests and a battery of language tests to assess language development, language processing, and pragmatic language. The results indicated that, under the age of 7, all children exhibited a number of autistic features (hand flapping, gaze avoidance, some tactile defensiveness, and abnormal use of language), and 30% qualified for a diagnosis of autism; by the age of 7, 85% qualified for a diagnosis of Asperger syndrome or "high functioning autism."

Deficits in social reciprocity have recently been asserted as the cardinal feature of Autistic Spectrum Disorders.<sup>20</sup> At the most fundamental level, successful engaging in reciprocal social interactions depends on two precursor abilities: social perception and social cognition, both of which appear to be impaired in those with PWS. Pictures representing the four emotions "scared, happy, angry, and sad" were presented to a group of children with PWS, and two additional groups of similar cognitive ability, one with a known genetic syndrome (Williams syndrome) and a group of children with cognitive impairments of unknown origin. With one exception, the children with PWS were less able to appropriately identify the emotion than were those in the other two groups. In the final instance, both the children with PWS and those with nonspecific mental retardation performed equally poorly and less well than those with Williams syndrome.

Social cognition was identified as an area of cognitive weakness in a study of 11 adolescents, aged 10.1 to 17.1 years, with PWS. Participants were asked to interpret the intention of characters in stories involving lies, jokes, and broken promises. Few of them were able to identify lies or jokes or to differentiate between a promise broken intentionally or unintentionally, which points to difficulties in interpreting non-literal language and social situations. Similarly, despite arguing that these behaviors signal a developmental arrest, both Clarke et al.<sup>18</sup> and Holland et al.<sup>58</sup> reported that these behaviors segregate with and correlate most strongly with autistic symptoms.

Recent genetic findings strongly support an autism-PWS association while suggesting that the PWS-OCD association may be exaggerated. Using ordered-subset analysis (OSD), Dementieva et al.<sup>27</sup> identified a homogeneous subgroup of families with Autistic Spectrum Disorders with a primary symptom complex described as "insistence on sameness." This complex includes three specific behavioral traits: (1) difficulties with minor changes in personal routine or environment, (2) resistance to trivial changes in the environment, and (3) compulsions/rituals. A second group was identified as those whose symptoms were primarily repetitive sensory and motor behaviors and interests. DNA studies of the "insistence on sameness" mapped the chromosomal abnormalities to chromosome 15q11–q13. A similar methodology investigated a group of "normal" individuals with diagnosed obses-

sive-compulsive disorder. These DNA studies mapped OCD to the X chromosome at the FRAXE site. Additional behavioral and genetic studies are needed to verify the PWS-Autistic Spectrum relationship; nonetheless Autistic Spectrum Disorders as a unifying framework for describing and understanding the behavioral complex associated with PWS appears promising.

### **Psychotic Symptoms, Psychotic Episodes, and Psychiatric Disorders**

The presence of psychiatric symptoms and multiple psychiatric disorders has long been associated with PWS<sup>8,55,67</sup> with both an incidence rate exceeding that found in a general population of those with mental retardation and with a predominance of those disorders falling in the psychotic disorder spectrum.<sup>16,46</sup> And, while research indeed suggests a slightly increased rate of psychotic illness in adults with PWS, the nature of this illness appears to be substantially different in character and duration than that found in a non-PWS affected population.<sup>19</sup> Indeed, one group of authors suggests that rather than traditional DSM-IV (*Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition) nomenclature, the term "PWS Psychiatric syndrome" is a more appropriate nomenclature for the thought disturbances associated with PWS.<sup>88</sup>

Bartolucci and Younger<sup>3</sup> describe three distinct neuropsychiatric symptom complexes associated with PWS. The first complex includes exaggerations of behaviors commonly associated with the syndrome, including oppositional tendencies, explosive episodes, and occasional antisocial tendencies. Because of the biological basis, environmental reactivity, and fluctuating nature of this complex, the authors term this complex a Trait Fluctuation (TF) disorder. While most affected individuals will normally exhibit fluctuations or ups and downs in the severity of these traits, for some this fluctuation has predictable cycles of occurrence and severity that exceeds normal ups and downs, and they may qualify as having a cyclical psychiatric disorder.

The authors define a second complex termed Lethargic-Refusal States, characterized by a withdrawing from usual activities and interactions, a refusal to eat or drink, a complete inattention to hygiene and self-care often accompanied by a nonorganic incontinence, and remaining totally bedridden. Not infrequently, there are disordered thoughts particularly around the possibility of food being purposely poisoned. These episodes are characterized by sudden onset, with a self-limiting course of several weeks and frequently spontaneous remission.

Finally, the authors describe Florid Psychotic States consisting of auditory or visual hallucinations, mood disturbances, and delusions accompanied by fear or occasionally abnormal elation. Subsequent investigations of those with symptoms in this latter group have led to the relabeling of this complex as atypical Cycloid Psychoses<sup>87</sup> and have raised speculation that those with a UPD subtype may be genetically more vulnerable to developing this disorder. Vogels et al.<sup>89</sup> sampled

an older PWS-affected group with known psychiatric problems. The group was divided into those with psychoses and those with mood disorders. The authors then conducted a retrospective review of early childhood behavior patterns and found that those with psychoses and either UPD or an imprinting center defect had an early childhood behavior pattern that was “active and extroverted.” Those with mood disorders, all of whom had the deletion form of PWS, had a childhood behavior pattern of “passive and introverted.” The authors note that these two behavior patterns are the extremes of a continuum. Many with PWS fall somewhere on a line between these two extremes. A subsequent population-based study in the U.K. found five young adults with PWS and psychoses. Since these young adults all were of the UPD genetic subtype, the assertion that UPD inevitably leads to psychoses has emerged.<sup>6</sup> What is unspecified in these studies, however, is how many of each genetic subtype were *not* affected with psychiatric difficulties. And, were there other commonalities besides genetic subtype among those who ultimately became ill?

To pursue psychoses as an inevitable outcome of a particular molecular subtype seems counterproductive. Indeed in the same article,<sup>87</sup> Verhoeven et al. also indicated that a subset of affected individuals with the deletion subtype appeared to be more vulnerable to serious mood disorders, among them bipolar disorder. While psychotic disorders are dramatic in presentation and call for immediate intervention, acute and recurring mood disorders are far more prevalent in this population<sup>28,96</sup> and may account for the majority of those described as the TF subgroup by Bartolucci and Younger. Clinical observations suggest that independent of a genetic vulnerability, the previously described cognitive rigidity, combined with difficulty labeling and expressing feelings and poor coping skills, may predispose those with PWS to an increased incidence of mood disorders, particularly when a major loss is involved. While genetic subtype may be associated with specific expressions of psychiatric difficulty, it seems much more fruitful to understand the nature of environmental stressors that catapult a small subset of individuals with PWS into these more serious psychiatric disturbances. Research regarding this association is ongoing.

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# Tools for Psychological and Behavioral Management

Barbara Y. Whitman and Kevin Jackson

Prader-Willi syndrome (PWS) continues to unfold as one of the more complex genetic syndromes. Most medical texts now identify PWS as an obesity syndrome, with accompanying cognitive deficits and behavior difficulties. Certainly the pervasiveness, severity, and impact of the food-related behaviors underscore this description. However, this characterization fails to recognize the primary role of the accompanying behavioral issues in the adjustment and management of affected individuals.

Behaviorally, the young child with PWS is described as happy, personable, affectionate, cooperative, and compliant, despite the emerging hyperphagia.<sup>7</sup> In direct contrast, however, by the time persons with PWS reach chronological adolescence, unless obesity is life-threatening, behavioral difficulties—often severe—become the central issue, both for individuals with the syndrome and their families.<sup>31</sup> While not universal, many by adolescence are described as ego-centered, moody, stubborn, manipulative, and prone to temper tantrums and rages that can result in injury to themselves and others. Emotional instability may appear as depression, obsessions, and frank psychoses. In many instances, these behaviors remain resistant to traditional behavioral and psychopharmacological management and can result in family turmoil, failure of both community living and meaningful employment, and may require mental health consultation, alternative living arrangements, and possibly even institutional placement.

Despite the presence of these behavioral features and their impact on the adjustment of affected individuals, there is a paucity of behavior management research on this population. With rare exception,<sup>12,28,61</sup> behavioral research is descriptive in nature, directed toward determining the presence (or absence) of specific behaviors, skills, or abilities, and the differential impact of the causal genetic mechanism (chromosome 15 deletion versus uniparental disomy) on these characteristics.<sup>8,10,24</sup> While critical for defining “typical” characteristics of affected individuals, these studies provide limited guidance regarding the day-to-day functioning of a specific individual and tend to underestimate the impact of environmental factors affecting behavior. In addition,

**Table 12.1. A Comparison of Normal Hypothalamic Functions with the Altered Physiologic Functioning Found in Prader-Willi Syndrome**

| Normal Hypothalamus       | Prader-Willi Syndrome                   |
|---------------------------|-----------------------------------------|
| Regulates appetite        | Hyperphagia                             |
| Sensitivity to pain       | Altered pain sensitivity (skin picking) |
| Regulates temperature     | Temperature instability                 |
| Regulates day/night cycle | Altered sleep/wake cycles               |
| Regulates emotions        | Emotional excesses                      |
| Impacts memory            | Short-term memory deficits              |
| Regulates breathing       | Central apnea                           |

many studies, in order to have a sufficiently large sample, include an age range encompassing infants through middle to late adulthood, measured at a single point in time.<sup>23,38</sup> Such a methodology makes it difficult to assess age-related behavioral shifts.

The primacy of hypothalamic dysfunction has long been asserted.<sup>33,34,39,59,70</sup> The role of the hypothalamus, juxtaposed against characteristics of PWS, highlights the basis for that assertion (Table 12.1). However, the documented range of intractable behaviors and neurocognitive deficits, coupled with neuroimaging studies,<sup>55,70</sup> indicate that Prader-Willi syndrome: (1) is a *pervasive* neurodevelopmental syndrome, and (2) reflects a distributed central nervous system dysfunction that has yet to be fully described either anatomically or biochemically. From this perspective, the centrally driven, food-related behavioral constellation, albeit dramatic, is just one of the neurobehavioral abnormalities attendant to this disorder and, when appropriately addressed, perhaps the easiest of the behavioral abnormalities to manage. This chapter will detail typical behavioral characteristics associated with PWS, examine critical issues, and offer strategies for effective management. To frame this discussion, it is necessary to briefly review the known neurobehavioral characteristics of affected persons that impact management. A more extensive review can be found elsewhere in this volume (see Chapter 8).

**Behavioral Overview**

**Food**

Despite a broad-ranging “typical” behavioral profile, Prader-Willi syndrome remains most readily noted for, and recognized by, an evolving constellation of abnormal food-related behaviors. Neonates typically demonstrate feeding difficulties and an accompanying failure-to-thrive that is, in part, attributed to the characteristic hypotonia (severe) and weak suck. Feeding aids, including special nipples, feeders, and even surgical supplementation, are routinely employed. Feeding difficulties, generally resolved by the toddler period, give way to an evolving constellation of eating concerns including extreme and constant (over)

eating, food foraging, food hoarding, preoccupation with food, manipulative and sometimes illicit behaviors directed at obtaining food, lessened liquid intake, and an accompanying aversion to activity even in the absence of obesity.

Part of the continuing (over)emphasis on the abnormal eating associated with PWS is historical. Early diagnosis for PWS is very recent. While the clinical constellation has been recognized since 1956, it was not until the late 1990s that testing provided the ability to genetically confirm the majority (99%) of those affected. Prior to that, diagnosis was often suspected, but delayed, until the emergence of the abnormal eating constellation and obesity. For those with a deletion, the average age at diagnosis was 6 years, and for those with uniparental disomy age 9.<sup>5</sup> Such diagnostic delays often led to an “intertwining” of the food-related behaviors with other behavioral components, so that the full range and impact of the behavioral profile as an issue, separate from the food-related behaviors, was not sufficiently appreciated. In fact, prior to the mid-1980s, uncontrolled obesity with the attendant health consequences was the central focus. Most affected individuals did not live beyond late adolescence or early adulthood. Fortunately, the advent of early diagnosis has allowed increased attention to weight management and the prevention of obesity for many (see Chapter 6). Additionally, the development of group homes specifically for those with PWS during the late 1980s and early 1990s has facilitated the development of effective weight reduction strategies, so that many affected individuals now live into middle and older age.<sup>41</sup> As weight and, concomitantly, health have become less of a central management focus, behavioral issues have become the central management focus.

### **Personality/Behavior and the Development of Behavior and Emotional Difficulties**

Like their nonaffected peers, individuals with PWS demonstrate a range of personality traits, talents, interests, strengths, and weaknesses.<sup>14-16</sup> In addition, the genetic alteration seen in this population may be specifically associated with a number of frequently challenging behavior and personality traits.<sup>29,38</sup> These traits and characteristics (termed a behavioral phenotype), while common among the majority of affected individuals (Table 12.2), may differ in severity between individuals, and may differ in severity in a single individual at different times.

Further, empirical data support clinical observation and parents' reports of a sequence of distinct behavioral/personality “epochs.”<sup>21,65,66</sup> As indicated, infants and young toddlers with PWS are usually described as cheerful, compliant, and cooperative. However, with the advent of emerging hyperphagia, several behavioral shifts occur, shifts that are independent of intellectual, language, or motor capacity.<sup>19,20</sup> This initial shift includes increasing oppositional tendencies, stubbornness, rigidity, increasing noncompliance, escalation in both food-related and other temper tantrums, shorter tolerance for frustration, overreaction to frustration, and a lessened ability to “go with the flow.”



**Table 12.2. Behavioral Comparisons of Those with Prader-Willi Syndrome and Cognitively Impaired Controls**

| Behavior                                                                                           | Percent Occurrence   |                               |
|----------------------------------------------------------------------------------------------------|----------------------|-------------------------------|
|                                                                                                    | Individuals with PWS | Cognitively Impaired Controls |
| Severe temper tantrums, e.g., stamps feet, slams doors                                             | 83                   | 26                            |
| Gets obsessed with an idea or activity                                                             | 72                   | 43                            |
| Scratches or picks his/her skin                                                                    | 89                   | 27                            |
| Eats nonfood items, e.g., dirt, grass, soap                                                        | 17                   | 14                            |
| Gorges on food; will do anything to get food (e.g., takes food out of garbage bins or steals food) | 72                   | 14                            |
| Stubborn, disobedient, or uncooperative                                                            | 85                   | 61                            |
| Cries easily for no reason or over small upsets                                                    | 77                   | 43                            |
| Shy                                                                                                | 13                   | 40                            |
| Underreacts to pain                                                                                | 65                   | 36                            |
| Moves slowly, underactive, does little (e.g., only sits and watches others)                        | 80                   | 31                            |
| Smells, tastes, or licks objects                                                                   | 39                   | 24                            |
| Tells lies                                                                                         | 74                   | 22                            |
| Sleeps too much                                                                                    | 54                   | 16                            |
| Steals                                                                                             | 59                   | 12                            |
| Upset and distressed over small changes in routine or environment                                  | 72                   | 45                            |
| Mood changes rapidly for no apparent reason                                                        | 63                   | 44                            |
| Kicks, hits others                                                                                 | 41                   | 41                            |
| Abusive, swears at others                                                                          | 52                   | 30                            |
| Impulsive, acts before thinking                                                                    | 59                   | 52                            |
| Tense, anxious, worried                                                                            | 46                   | 35                            |
| Thoughts are unconnected, different ideas are jumbled together, etc.                               | 35                   | 28                            |

Source: Adapted from Einfeld et al., *American Journal of Medical Genetics*, 1999.<sup>29</sup>

Youngsters exhibit increased difficulty with transitions, even from one activity to another, and develop special routines and rituals that are difficult to avoid or circumvent. For many, attentional deficits are also noted.

A second shift is noted somewhere around 7 to 8 years of age with an escalation of previous patterns and a significantly increased rigidity of behavior,<sup>1,14</sup> including the tendency to “get stuck” on a thought or question, further evidence of attentional deficits impacting academics and behavior, increased worrying about both real and imagined problems, less response to redirection, and less benefit from “time out” and “calming” efforts. The need for invariance is noted along with excessive reactivity to changes in this structure and routine. A falling behind age-matched peers in social skills and the beginning of a chronic anxiety also become evident.

Finally, another shift is associated with the chronological onset of adolescence. The impact of chronic anxiety becomes clearly evident. Increased mood instability frequently is coupled with more outwardly directed expressions of frustration and anger. Immaturity, in the form of insistence on having one’s way, regardless of the environment or others affected, often leads to social and relationship problems. For

many, there is a continuing increase in reactivity to real or imagined hurts and injustices, and for some, frank emotional and thought disorders. These behavioral epochs occur in both males and females and appear to be independent of cognitive ability and BMI (body mass index).

Recent behavioral studies debate whether the constellation of repetitive speech, special routines, rituals, and skin picking are indicative of a specific psychiatric diagnosis,<sup>26,57</sup> whether the development of these behaviors and psychiatric difficulties is inevitable,<sup>4</sup> and whether an individual's causal genetic mechanism (i.e., deletion vs. uniparental disomy) implies increased risk for these behaviors.<sup>38</sup> Ultimately, these studies aim for a more parsimonious match between problem behaviors and intervention, including medication. To date, however, that yield has been sparse, with most research providing few guidelines for intervention in these behavioral symptoms. There are a number of reasons for this sparseness. First, while many people with the syndrome exhibit a broad range of behaviors that are problematic and unresponsive, in general these behaviors and "symptoms" do not meet criteria for a formal psychiatric diagnosis.<sup>11</sup> Moreover, while most affected individuals demonstrate a constant "baseline" of difficult behaviors that, with patience, are manageable by families without specific intervention, most do, at some point, acutely exhibit more severe behavior problems and outbursts. Often problematic behaviors are limited to a single environment (e.g., school only, home only, workshop only); when the problematic environment is addressed, the behaviors return to baseline. While many affected individuals may have episodes of extreme emotional disruption, and for some that disruption may become chronic, it remains unclear how much of this disruption (if any) is a direct function of Prader-Willi syndrome. It seems clear that affected individuals are more vulnerable to stresses that can lead to emotional disruption, but whether the disruption is differentially intensified due to the underlying genetic influence of Prader-Willi syndrome on emotional reactivity, or whether the disruption is simply a reaction to the concurrent pressures of having Prader-Willi syndrome in combination with environmental difficulties, remains unspecified. There is general evidence that an alteration of the genetic structure and the subsequent altering of neurobehavioral functioning may include an alteration in the way the affected individual perceives and responds to routine environments, normal stresses, and standard reward and punishment strategies. Systematic study of the proclivity toward emotional reactivity, specifically in persons with Prader-Willi syndrome, would be very helpful. An issue to be addressed later is the use of behavior change medication for this group, since a number of risks including an escalation of appetite may be incurred.

## Cognition

While the characteristics of PWS include cognitive impairments, primarily mild mental retardation, data document a wide range of intelligence scores among affected individuals. When the findings of a

number of studies are pooled, the following percentages emerge: Normal 4.9%, Borderline 27.8%, Mild Mental Retardation 34.4%, Moderate Mental Retardation 27.3%, and Severe to Profound Mental Retardation 5.6%.<sup>13</sup> However, tested IQ scores yield an inflated estimate of ultimate behavioral performance. Several additional factors further depress both academic performance and overall adjustment. First, even when tests indicate IQs in the normal range, cognitive abilities and learning capacities are unevenly developed. Difficulties in understanding and using language have an additional negative impact on cognitive functioning. Studies document deficits in vocabulary, receptive and expressive language, language comprehension, pragmatic language, poor discourse and conversational skills, and shortened length of utterances.<sup>46</sup> Problems in short-term memory as well as learning tasks that are sequential in nature present challenges that are often insurmountable.<sup>25</sup> Most affected individuals remain extremely concrete, rigid, and rule-governed in their thinking, lacking the capacity to develop abstract thinking and concepts. Collectively, these cognitive difficulties impact daily behavior and the overall ability to adapt.

*How do these deficits impact day to day behavior?* The term *mental retardation* indicates a slower-than-average “rate” of learning, a characteristic that is observed in persons with PWS across all levels of cognitive ability. In addition, it implies a slower-than-average rate of “processing” routine tasks, another phenomenon frequently observed in those with PWS—particularly when responding to precise verbal demands. Thus, if asked a question and rushed to provide an answer, there is often an observable increase in anxiety and frustration. If this happens several times in close succession, increased frustration may escalate to acting out.

Further, persons with PWS—though frequently highly verbal—often have difficulty explaining their actions. Even when behaviors are reasonable, affected individuals are frequently unable to articulate an explanation, escalating their frustration and raising the risk for aggression. Moreover, language-processing difficulties combined with slower processing may result in an individual’s grasping only the initial elements of a conversation or set of instructions while additional aspects of the ongoing interaction are missed.

Sequential processing deficits<sup>25</sup> add further complications. Persons with sequential processing deficits have difficulty telling time and comprehending temporal order (days of the week, months of the year), have difficulty integrating elements into temporal or sequentially ordered groups, and have trouble following a schedule or sequence, such as difficulty remembering what to do and when to do it. Figuring out the order in which to tackle the components of a task is usually an ordeal for them.<sup>64</sup> An inability to figure out what needs to be done and the order in which it must be done—especially if the task is not part of the learned, daily, predictable routine—leads to a constant state of being overwhelmed and anxious, with an increased vulnerability to even minor stresses (e.g., being rushed to change from one task to another). Finally, an inability for abstract thinking is reflected in poor social relationships. Persons with PWS recognize only a limited number

of emotions, perhaps as few as two to three emotions along a continuum from extremely happy to very sad. Limited recognition of their own as well as others' emotions, coupled with difficulty in understanding another's point of view,<sup>58</sup> predictably leads to problems getting along with others. Those who understand the world only in terms of "I want" or "I don't want" have difficulty with the social conventions and reciprocal behavior necessary for relationships. In sum, this combination of cognitive difficulties leads to difficulties learning and getting along with others. Since the management of the food-related behaviors is, in many ways, the easiest of the behavioral difficulties to manage, we turn to that issue first.

## Managing the Food-Related Behavioral Constellation

### Medication

One of the many complexities associated with Prader-Willi syndrome is the continuing unresponsiveness of the hyperphagia to conventional pharmacologic intervention. One stream of evidence suggests that the hyperphagia associated with PWS results from a central nervous system failure to signal satiety, rather than traditional hunger mechanisms. This implies that affected individuals are always hungry because they never feel full.<sup>36,37</sup> While some authors locate this failure in the hypothalamus, other authors postulate that dysregulation of one or more specific neurotransmitters causes the hyperphagia<sup>17,30,48,59</sup>; a variety of medications targeting these neurotransmitters demonstrate only spotty success. Currently there are two broad categories of approved pharmacologic interventions: (1) those that decrease food intake by reducing appetite or increasing satiety by their action on central nervous system neurotransmitters (appetite suppressants), and (2) a newer group of those that decrease nutrient absorption by their action in the gut.<sup>69</sup>

Historically (i.e., in the 1960s and 1970s), affected individuals were routinely prescribed appetite-suppressing amphetamines; however, their use was discontinued when they proved ineffective against the hyperphagia while often causing significant behavioral side effects.<sup>67</sup> A more recent group of appetite-regulating medications includes fenfluramine, phentermine, and sibutramine (Meridia). Selikowitz et al.<sup>52</sup> reported statistically significant weight loss in 8 of 15 patients participating in a doubly blinded treatment/placebo study of fenfluramine. A closer examination of the data indicates that 2 of those 8 also lost weight during the placebo portion of the study. Two other participants neither gained nor lost weight during the placebo period but gained weight during the medication trial. Subsequent safety concerns, however, excluded the use of both fenfluramine and phentermine. The side effects of sibutramine as well as those of absorption blockers such as orlistat, make them impractical for the extended use needed by those with PWS.

Based on the theory that the hyperphagia results from increased brain endorphins, Zlotkin et al.<sup>71</sup> tested the appetite-suppressing effects of naloxone in four adolescents with PWS, with no significant effect.

Thus until a safe and effective medication becomes available, management of the food-related aspects of the syndrome remains primarily behavioral and environmental. For nutritional management information and further discussion of appetite research, see Chapter 6.

### **Behavioral and Environmental Management**

Experience of the past two decades has been instrumental in developing effective strategies for managing both weight and the accompanying food-related behavior constellation. Much of this understanding comes from two populations of young adults entering group living settings: (1) young adults whose weight has been well managed and who have never been obese, and (2) young adults who, prior to out-of-home placement, have been extremely obese. This experience underscores that, of the challenging behaviors associated with PWS, the food-related behavioral constellation is the easiest to manage.<sup>38</sup> Simply put, effective management requires the unyielding presence of four elements: (1) a physical environment structured so that food access is completely eliminated, (2) an appropriate dietary and exercise plan, (3) a procedure for ensuring that the affected person is always informed regarding the time and menu for the next meal or snack, and (4) elimination of all other avenues for obtaining food. Where such stringent management is new, the person with PWS may initially act out and attempt to dismantle all boundaries. For many, such behaviors have previously proven effective in undermining management attempts. However, with consistency and patience, this period of acting out usually subsides. Even when behavioral compliance has been accomplished, frequent conversations about food may continue. Many routinely ask what will be served at the next meal, ask when the next meal will be served, ask how the food will be prepared, ask “Is it time yet?”, complain that there isn’t enough food, and request additional portions. Nonetheless, with management that is both consistent and stringent, behavior eventually stabilizes and cooperation and compliance are less difficult to obtain. Parents and caregivers report that, over time, when the person with PWS realizes that excess food is no longer available, many appear to experience a marked reduction in anxiety and report feeling safer, knowing the limits are effective and inviolable.

Thus, while extremely simple in concept, total elimination of food access can be extraordinarily difficult to accomplish, because to do so requires eliminating food and money accessibility *in every environment*, including access to vending machines or even the remotest possibility of surreptitiously “running down the street to get a Coke.” Food of one type or another is regularly found in virtually all human environments—classrooms, school buses, cars, offices, gymnasium dressing rooms, parking lots, playgrounds, and anywhere a trash can is present. Furthermore, many groups routinely fund-raise with some food product: band candy bars, Girl Scout cookies, and fruit cakes and pecans during the holidays are some that may be more difficult to avoid. To fully “food-proof” an environment, it may be necessary to

lock cabinets, refrigerators, doors to the kitchen, and garbage cans and to alter traffic patterns for delivering groceries. And, while a family or caregiving setting may be able to make these alterations, equally important, but often more difficult to manage, are additional environments where the affected person may spend time, such as schools, workplaces, recreational programs, churches, and shopping malls. Individualized Education Plans (IEPs) and Individual Habilitation Plans (IHPs) should specify the needed environmental safeguards as part of the plan. However, it is rarely enough to merely specify that environments should be food-free, even when those managing the various setting are fully cooperative. Even the best-intentioned schools, churches, or workplaces will find it challenging and sometimes impossible to eliminate food. For this reason, affected individuals often require the assistance of an aide or increased supervision of some form to prevent food access. While vigilance and awareness is always necessary, there will inevitably be slips that should be handled matter-of-factly and subsequent dietary intake adjusted. Even in well-monitored environments it is essential to educate caregivers to detect pursuit of food and to deter the inevitable and often clever pursuit of food.

### Using Food as a Reinforcer

In addition to social praise and attention, a variety of non-food items and privileges can effectively serve as reinforcers for most individuals. However, when several behavior change plans have proven ineffective, the possibility of using food reinforcers is inevitably raised. There currently are several points of view regarding this issue.

One point of view assumes that the nutritional management of PWS is analogous to, and as critical an issue as, the dietary management of diabetes. Therefore, appropriate management includes a restricted diet developed in consultation with a nutritionist or clinical dietitian and the primary care physician. The degree of restriction hinges on individual need; those needing to lose weight may require a more restricted caloric intake, while those needing to maintain weight or who are still in a growth phase may require a less restricted diet. A number of other variables impact caloric requirements, such as energy expended through exercise, use of supplemental growth hormone therapy, and the presence of diabetes. This point of view considers the use of food as a reinforcer “out of bounds.” It assumes that such an approach is confusing and undermines the critical medical aspect of dietary requirements. Thus it follows as an absolute that any food that is *outside* the dietary and medical treatment plan cannot be used as a reinforcer. For example, a school setting that allows an “extra” Coke, candy bar, or ice cream to obtain compliance or alter behaviors would be considered both unsafe and inappropriate.

However, there are ways within this frame of reference to effectively use food as a reinforcer, when safely incorporated within the dietary and medical treatment guidelines. For example, individuals with Prader Willi syndrome rarely eat indiscriminately and have individual food preferences that remain constant.<sup>40,42</sup> Appropriately structured,



these preferences can be employed as reinforcers. Thus allowing a preferred (and allowable) breakfast food choice (e.g., Cocoa Puffs) can be made contingent on timely completion of a prespecified behavior (e.g., being up, dressed, and ready for school on time). Similarly, special restaurant visits or trips to a store to purchase a food item may be used as a one-time reinforcer or on a regular schedule based on meeting certain specific behavioral goals over time (e.g., being up on time for school each day). In some instances, very low-calorie food items such as sugar-free candies, drinks, or gum may serve as strong reinforcers without significant impact on overall caloric consumption.

In the case of critically important behavior, a specific portion of daily calories may be allocated for use as reinforcement. For example, Keefer<sup>42</sup> examined the exercise behavior of seven individuals with Prader-Willi syndrome. None of the participants in this study exercised during baseline observations. Initially, most of the subjects engaged in some exercise with just verbal prompting. However, even with verbal encouragement, exercise participation diminished over a period of a few days for all but one individual. In phase two, the remaining six individuals were then provided with either extra calories (usually 100 calories) to be used at their discretion or specific extra food items based on completing exercise requirements. All of these participants resumed exercise and ultimately met the program goal of exercising continuously for 45 minutes, three times a week, and their hearts remained in a beneficial aerobic zone. One individual who weighed 500 pounds at the start of the study lost 180 pounds during the course of the project. Notably, no negative behaviors were observed associated with program participation. Predictably, there were problem behavior incidents from participants who exercised but whose efforts failed criteria for earning extra calories. There were no reports of obsessive verbalizing about the exercise or calories being earned.

A different point of view holds that, when used appropriately, and integrated into the overall dietary plan, food is an especially powerful reinforcer in this population. Thus, holders of this view assert that it would be a disservice to fail to take advantage of edibles as a reinforcer when either addressing problem behaviors previously resistant to change or when establishing critical behaviors such as exercise or cooperation with medical procedures or therapies. Since food is an especially powerful reinforcer, therefore, its use for reinforcement should be reserved for priority behaviors.

However, even those who embrace this point of view assert that *any* use of food as a reinforcer should be approached with caution, since the effects of any reinforcement procedure depend on establishing an appropriate link between the desired behavior and the reinforcer and reliably implementing the procedure. To avoid reinforcing inappropriate behavior, food should never be provided in the midst of a behavior incident as a means of stopping the behavior or gaining compliance. Similarly, food should never be provided in response to a threat (e.g., "Give me food or else."). Correct use of food as a reinforcer requires documentation that the individual can perform the desired behaviors. If appropriately designed, the reinforcer will be earned more often than

not. The reinforcement plan should be discussed in advance with the participant at a time and place away from any behavior problem incident and in a private location free from interruption. When individuals participate in the development of their own behavior plan, there is greater compliance and an increased likelihood of success. To insure that the plan is clear to the participant, it is helpful for the individual to restate the plan, specifying the expected behavior and the consequences for meeting and not meeting expectations.<sup>45</sup> A written behavior contract can be an effective method for setting up such plans.

## General Strategies and Approaches to Intervention

Successful behavior management requires at least three elements: (1) a consistent, supportive environment; (2) strategies for promoting positive behavior; and (3) tools for changing difficult behavior.

### Environment

It has long been accepted that much of our behavior is influenced and controlled by the environment—both physical and social. It has also been established that many individuals with genetic disorders have altered and often skewed perceptions of the environment. That those with PWS are extremely sensitive and reactive to the environment also has long been clinically accepted and seems only logical when the impact of multiple cognitive/learning deficits on day-to-day functioning is considered. In addition to heightened environmental sensitivity, persons with PWS tend to overreact to and overemphasize the negative aspects (real or imagined) and underreact to the positive aspects of the environment. Thus the role of the surrounding environment in supporting or impeding positive behavior management and positive adjustment for those with PWS cannot be overemphasized.

Research documents that family environments (as well as school, vocational, and group home/supported living settings) can be characterized on a continuum ranging from chaotic to flexible, structured, and ultimately rigid.<sup>35,49</sup> Both flexible and structured environments are most effective when an individual's neurologic status allows reasonable levels of flexibility or an ability to "go with the flow." Both chaotic and extremely rigid environments are, at a minimum, unsupportive and can be totally unsuitable. As individual flexibility decreases, the need for more highly structured and predictable environments increases. The reduced capacity of those with PWS to be flexible, an inherent neurologically based reactivity, and an inability to employ sequential problem-solving strategies dictate that environmental structures that are routine, predictable, and consistent best minimize frustration and reactivity. This structure should include (1) those inviolate "family and house rules" regarding what is expected, acceptable and unacceptable behavior, along with specified consequences for misbehavior that are consistently administered; and (2) schedules that are, as much as possible, invariant in time and task routines. Consistency between parents or caregivers is critical since inconsistency invites frustration and acting

out. In addition, the structure must anticipate and provide carefully designed opportunities for the individual to make choices. A simple example will illustrate. If Mom asks, "What do you want for breakfast?" in an open-ended fashion, it suggests (1) that all choices are valid and available and (2) that any choice will be provided. When the answer is "chocolate cake," the obvious response from Mother is, "You can't have chocolate cake for breakfast!" To the person with PWS, the offer implying an open-ended choice, followed by a denial of the selected choice, is confusing and *feels punitive*, raising the probability of a reactive tantrum. However, if Mom asks, "Do you want eggs or oatmeal for breakfast?" she is still offering a choice but one that is positively structured within the dietary plan, while at the same time providing the affected person with a choice and a sense of personal control. For both Mother and the person with PWS, the choice has been structured as a win-win outcome. In the event that the person with PWS answers, "I want (something different)," Mother has two options. She can respond, "That was not one of the choices; you need to pick either eggs or oatmeal," or she can respond, "OK, just for today I'll allow another choice." Whether Mother allows a different choice this one time in part depends on Mother's previous experience with this child and her assessment of whether granting this one exception is likely to lead to perseverative pleading for more exceptions. When as many positively structured choices as possible are a routine part of daily living, many areas of power struggle and frustration are avoided.

### Strategies for Changing Behavior

Appropriately utilized, behavior analytic procedures can be successful in addressing behavior concerns in Prader-Willi syndrome.<sup>3</sup> Most published reports have focused on food-related behaviors,<sup>2,50</sup> but success has also been documented with other behaviors.<sup>6,27</sup> The success of behavioral interventions hinges on the ability of caregivers to provide the necessary intervention with consistency and integrity. In some cases a more technical and professionally designed behavior change program may be necessary to produce an acceptable behavior improvement. This section begins by describing general behavior analytic principles and change strategies, and then focuses on the application of these principles to those with PWS.

The behavioral approach is based on changing the consequences of behavior. The most successful behavioral approach includes a general strategy of emphasizing (or giving positive consequences for) positive social interactions and eliminating coercion.<sup>45</sup> Examples of coercion include questioning, arguing, threatening, using verbal or physical force, criticism, and taking away privileges. Research has shown that many problem behaviors are maintained by social attention and that positive attention can be a powerful consequence for strengthening appropriate behavior.<sup>44</sup> Coercion may stop a given instance of a problem behavior in the short run but, over time, makes things worse. Coercion motivates the desire to escape and to avoid the people and circum-

stances associated with the coercion. It can also directly trigger inappropriate emotional behavior and often motivates the individual to retaliate or get even with people and places associated with the coercion. These common effects of coercion may be heightened in individuals with Prader-Willi syndrome, who are known for their emotional lability. Coercion also provides social attention to problem behaviors, for many with Prader-Willi syndrome serving as an unintended, *positive* consequence, thereby directly strengthening these behaviors. It is well documented that, when used long-term, coercive social environments are highly predictive of antisocial behavior and other undesirable effects in children.<sup>54,62</sup> Coercion also provides a model of inappropriate behavior that may later be imitated.

The “praise and ignore” or “pivot” tool illustrates a positive change approach. Pivoting involves the use of attention as a reinforcer of appropriate behavior. The pivot tool involves (1) attending to (with praise or physical contact) appropriate behavior on a regular and consistent basis, while (2) ignoring harmless inappropriate behavior. When inappropriate behavior occurs, the strategy is to pivot attention away from the problem behavior to another task or the appropriate behavior of another individual, wait patiently for the targeted individual to engage in some appropriate behavior, then pivot attention and praise back to the individual. For example, if a child is asked to perform some task and responds with resistive arguing, the parent would immediately pivot attention to some other activity and wait until the child begins to do the task, then immediately praise the child while verbally acknowledging the appropriate behavior.

If a desired appropriate behavior is occurring too infrequently to provide sufficient opportunities for reinforcement, the “reinforced practice” tool can be used. This tool is especially appropriate for addressing tasks that the individual with Prader-Willi syndrome may have been consistently resistive to completing. The steps of this tool are: (1) decide what the individual is expected to do, (2) provide opportunities to learn and practice the behavior repeatedly with reinforcement, and (3) reinforce the behavior when it occurs in the real situation. For example, suppose a parent wants the child to carry his/her school materials into the bedroom after school each day instead of just dropping these items inside the door. The parent waits for a time when they both are calm and in a good mood. The parent then (1) introduces the topic in a positive way using actual school materials and (2) has the child pretend he/she is just arriving from school and (3) practice putting the materials in the bedroom. As soon as the behavior occurs, the parent (4) reinforces the behavior by, for example, delivering exaggerated praise, emphasizing that the child has done exactly what the parent expects. These steps should be repeatedly practiced, with reinforcement provided each time the sequence is appropriately performed. To be sure that the youngster fully understands what is being asked, the child should be asked to verbally restate what behavior is expected and when it is to occur. Following the practice session, the parent must closely observe the child the next time he/she returns from school; if the practiced behavior occurs, it should occasion enthusiastic praise.

Once the behavior has occurred a couple of times, it may not be necessary to provide praise at each occurrence of the behavior. If the behavior deteriorates unacceptably at a later time, the parent simply repeats the practice tool.

In addition to praise and attention, individual preferences usually offer a variety of other items or privileges that can successfully reinforce appropriate behavior.<sup>45</sup> Such tangible reinforcers are usually reserved for behaviors that are resistive to change or involve a greater amount of work (e.g., vacuuming several rooms).

Another powerful tool for making use of such reinforcers is the "behavior contract." A behavior contract is a written agreement that an individual will earn a desired item or privilege, based on the occurrence of a specifically defined behavior. Behavior contracts are usually used to address persistent problem behaviors, establish new responsibilities, or improve performance when the individual's responses have been inconsistent. For example, if an individual with Prader-Willi syndrome has trouble getting up and getting ready for school in the morning, and prompting this behavior often leads to tantrums, a contract may be helpful in addressing the morning routine. A contract must specify all tasks to be completed, completion times (e.g., fully dressed and in the kitchen by 7:15 a.m.), and other attitudinal or behavioral parameters (e.g., speaking with an inside voice rather than yelling, as in a tantrum). The contract should also specify a daily consequence for completing these tasks (e.g., sticker on a wall chart) and a long-term consequence (e.g., trip to the pet store) for consistent completion of these tasks (e.g., 4 out of 5 weekdays). Once the behavior is occurring consistently, the tangible reinforcer can be used to address another behavior and the original behavior can be maintained by the occasional praise and more natural consequences.

Dangerous behavior or behavior that is too disruptive to ignore can be addressed with the "stop-redirect-reinforce" technique. This tool requires (1) immediate termination of the behavior by interrupting it verbally and physically, (2) verbal redirection to an appropriate behavior (related, if possible), and (3) immediate provision of positive attention when the redirected (or any appropriate) behavior occurs.

For behaviors that have not responded well to other attempts at change, or when the process of stop-redirect-reinforce has been unsuccessful, "time-out" (i.e., time-out from positive reinforcers—not to be confused with the usual use of the term) may be used. Time-out is a specific detailed protocol that, when correctly employed, can be part of a very effective plan for eliminating serious problem behavior. Time-out should only be used with an individual that can be controlled physically by those expected to implement the time-out. Time-out will not be effective if improperly implemented, as often occurs. When first used, time-out often produces a burst of resistive or aggressive behavior. In some cases this may be so severe that the intervention cannot be used. It is recommended that a reliable reference<sup>45</sup> be consulted in developing a plan for use of time-out. Table 12.3 lists general behavioral analytic tools appropriate to specific categories of problem behaviors often demonstrated by persons with Prader-Willi syndrome. Table 12.4 details a number of specific behaviors associated with Prader-

Table 12.3. Problem Behavior Categories and Tools for Dealing with These Behaviors

| Problem Behavior                                                                                                                                       | Behavior to Increase or Reinforce                               | Behavioral Tool(s)                                                                                                                          |
|--------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------|
| Annoying behavior that is physically harmless                                                                                                          | Playing appropriately                                           | Pivot (praise and ignore)                                                                                                                   |
| Arguing                                                                                                                                                | Beginning, working on, or completing a task                     |                                                                                                                                             |
| Minor skin picking                                                                                                                                     | The absence of any problem behavior                             |                                                                                                                                             |
| Not complying with a request (occasional)                                                                                                              |                                                                 |                                                                                                                                             |
| Not complying with a type of request (regularly)                                                                                                       | Complying with the specific type of request targeted for change | <ul style="list-style-type: none"><li>• Pivot (praise and ignore)</li><li>• Reinforced Practice</li><li>• Behavior Contract</li></ul>       |
| Not performing some assigned task or activity consistently                                                                                             | Performing the assigned task or activity                        |                                                                                                                                             |
| Disruptive behavior that cannot be ignored                                                                                                             | Specific appropriate behavior                                   | <ul style="list-style-type: none"><li>• Stop-Redirect-Give Positive Consequences</li></ul>                                                  |
| Dangerous behavior, or a behavior that occurs in a situation that in the past has resulted in dangerous or disruptive behavior, that cannot be ignored | A positive behavior routine that is expected to occur           | <ul style="list-style-type: none"><li>• Time-out (not for skin picking)</li><li>• Reinforced Practice</li><li>• Behavior Contract</li></ul> |

Willi syndrome and specific behavioral analytic techniques that have proven successful for managing those behaviors at home and school.

The Use of Medication for Behavior Management

The use of psychotropic and neuroleptic medications (medications designed to alter behavior, mood, or thought by targeted action on brain chemistry) is increasingly advocated to (1) supplement behavior management strategies or (2) as a primary intervention in the case of severe emotional or cognitive disruption (e.g., depression, psychosis). The use of these medications in this population remains one of the more controversial management strategies, due in part to a paucity of research in this area. With little empirical data to guide clinical decisions, many clinicians have developed prescribing practices based on individual clinical experience. Widely differing, often contradictory experiences with similar medications and dosages result in vastly differing clinical opinions regarding medication use in general and regarding specific medications. An additional source of controversy is lodged in the assertion that medication is frequently used as a substitute for good behavior management, particularly for difficult and challenging behaviors, and particularly in community living settings. This assertion is not unfounded,<sup>47</sup> further complicating decisions regarding medication use in this population.

Given the importance of this issue, it may seem strange that there is so little research in this area. However, this lack of data begins to make



Table 12.4. Behavior Management Strategies for Home and School

| Common Behavior Characteristics in Youngsters and Adults with PWS                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | Possible Management Strategies                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
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|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | Home                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | School                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
| <p><i>Rigid Thought Process and Inability to Be Behaviorally Flexible</i></p> <p>Youngsters and adults with Prader-Willi syndrome have a hard time being flexible and accommodating changes of schedule and routine. It is also common for people with PWS to receive and store information in a single order, so that they must go through the whole order to get any one piece. Thus, there is a strong need for routine, sameness, and consistency in the learning environment. Because of a problem in sequence processing, students are not always able to turn <i>what not to do</i> into <i>what to do</i>.</p> | <ul style="list-style-type: none"> <li>• Provide weekly and daily schedules in visual form.</li> <li>• Provide verbal anticipation of changes and allow for discussion. Do this in a safe area where person with PWS can share feelings. (The youngster needs time to adapt to this change.)</li> <li>• If there is a change, use visuals; put things in writing—lists, schedules (correct when changes are made).</li> <li>• Don't make promises you can't keep.</li> <li>• Break down tasks and activities into concise, orderly steps. For many youngsters it is helpful to provide pictures of the youngster/adult performing tasks and activities.</li> <li>• To resolve "stubborn issues" try using compromise. Both the parent/caregiver and the youngster/adult have to come up with a totally new solution. Not only is this a successful problem-solving strategy—it can also be a form of diversion.</li> <li>• Provide praise when being flexible.</li> </ul> | <ul style="list-style-type: none"> <li>• Provide weekly and daily schedules in form and, where needed, pictures of the youngster/adult performing tasks and activities.</li> <li>• Provide verbal anticipation of changes and allow for discussion. Do this in a safe area where they can share feelings. (The student needs time to adapt to this change.)</li> <li>• If there is a change, use visuals; put things in writing—lists, schedules (correct when changes are made).</li> <li>• Don't make promises you can't keep.</li> <li>• If able, communicate changes in personnel ahead of time—but not too far ahead.</li> <li>• Break down tasks and activities into concise, orderly steps. For many youngsters it is helpful to provide pictures of the youngster/adult performing tasks and activities.</li> <li>• To resolve "stubborn issues" try using compromise. Both the student and the educator have to come up with a totally new solution. Not only is this a successful problem-solving strategy—it can also be a form of diversion.</li> <li>• Provide praise when being flexible.</li> </ul> |
| <p><i>Perseverative or Obsessive Thinking</i></p> <p>This is the tendency to get "caught" on one thought, question, or issue—to the point where it overshadows all other thoughts and activities.</p>                                                                                                                                                                                                                                                                                                                                                                                                                  | <ul style="list-style-type: none"> <li>• Use reflection—have youngster/adult restate what you said.</li> <li>• Put in writing; use visuals. Carry a small notebook if needed.</li> <li>• Less is best—give one direction at a time and allow completion before the next direction.</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | <ul style="list-style-type: none"> <li>• Use reflection—have student restate what you said.</li> <li>• Put in writing; use visuals. Carry a small notebook if needed.</li> <li>• Less is best—give less amount of work at one time rather than more. Add to the work as time allows.</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |

This behavior can contribute to difficulty in transitioning from one topic/activity to another. Since affected individuals often have a great need to complete tasks, if they are stuck it can lead to loss of emotional control.

*Tenuous Emotional Control or Short Frustration Tolerance*

Any combination of life stressors can lead to emotional “dyscontrol.” The result may be exhibited as challenging behaviors such as tantrums—yelling, swearing, aggression, destruction, self-injury.

During these episodes, the ability to reason is overridden by emotion.

- Avoid power struggles and ultimatums.
  - Ignore (if possible).
  - Don’t give more information than is necessary, especially too far in advance.
  - Use “strategic timing”—schedule an activity that the youngster/adult has difficulty ending for right before snack or lunch.
  - Set limits: “I’ll tell you two more times, then we move on to next topic. This is #1.”
- Be aware of “person/environment overstimulation”—for instance large family gatherings, church settings, malls, grocery stores, etc. Have a previously practiced time-out procedure to allow calming down when getting overstimulated and give praise for using.
  - Start the day off on the right foot by allowing time to go over the schedule for the day and work through any changes there may be. Putting the new schedule in writing often helps to decrease anxiety.
  - At the start of the day, set daily behavioral expectations with the youngster. Limit to no more than 3. Communicate behaviors *you wish to see*. Make it a cooperative task that provides concrete behavior expectations. Put goals in writing. Avoid the word “Don’t” . . . focus on the word “will” (e.g., “I *will* talk in a quiet voice” . . . instead of “Don’t yell.” “When I feel frustrated, I *will* tell Mr. Smith or another adult.”)
- Avoid power struggles and ultimatums.
  - Ignore (if possible).
  - Don’t give more information than is necessary, especially too far in advance.
  - Use “strategic timing”—schedule the activity that the student has difficulty ending for right before snack or lunch.
  - Set limits: “I’ll tell you two more times, then we move on to next topic. This is #1.”
- Be aware of “hallway overstimulation”—especially before the school day begins. Have student enter the building at a less popular entrance. If possible, have arrival time be 5–10 minutes after school starts. Dismiss early.
  - Start the day off on the right foot by allowing time to go over the schedule for the day and work through any changes there may be. Putting the new schedule in writing often helps to decrease anxiety.
  - At the start of the day set daily goals *with* the student. Limit to no more than 3. Communicate behaviors *you wish to see*. Make it a cooperative task that provides concrete behavior expectations. Put goals in writing. Avoid the word “Don’t” . . . focus on the word “will” (e.g., “I *will* talk in a “quiet voice” . . . instead of “Don’t yell.” “When I feel frustrated, I *will* tell Mr. Smith or another adult.”)

(Continued)

Table 12.4. Behavior Management Strategies for Home and School (*Continued*)

| Common Behavior Characteristics in Youngsters and Adults with PWS         | Possible Management Strategies                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
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|                                                                           | Home                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | School                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| <i>Tenuous Emotional Control or Short Frustration Tolerance—continued</i> | <ul style="list-style-type: none"> <li>• Provide positive attention and praise when youngster/adult is maintaining control, especially in difficult situations. Celebrate success!</li> <li>• Encourage communication and acknowledging feelings. Words are important—Listen carefully!</li> <li>• Include the student in behavior plans. Having their input elicits cooperation and a sense of support.</li> <li>• Be a role model: “I always say ‘darn’ when I am angry. Let’s try that for you . . . darn, darn, darn.” Practice when the youngster/adult is <i>not</i> agitated or angry.</li> <li>• Depending on the youngster/adult and the situation, use humor. It is often effective.</li> <li>• Similarly to the process for overstimulation, anticipate build-up of frustrations and help him/her to remove self to “safe area.” Create a key word or phrase that will alert the student that it is time to go. Practice using these words/ phrases when the student is calm.</li> <li>• Develop a plan and rehearse with the youngster/adult <i>what to do</i> if he/she feels angry or frustrated. Many students substitute a means of releasing this pent-up anger—long walks/exercise, ripping paper, tearing rags, popping packaging bubbles.</li> <li>• <i>Don’t try reasoning when student is out of control. Limit discussion.</i></li> </ul> | <ul style="list-style-type: none"> <li>• Provide positive attention and praise when student is maintaining control, especially in difficult situations. Celebrate success!</li> <li>• Encourage communication and acknowledging feelings. Words are important—Listen carefully!</li> <li>• Include the student in behavior plans. Having their input elicits cooperation and a sense of support.</li> <li>• Be a role model: “I always say ‘darn’ when I am angry. Let’s try that for you . . . darn, darn, darn.” Practice when the student is <i>not</i> agitated or angry.</li> <li>• Depending on the student and the situation, use humor. It is often effective.</li> <li>• Anticipate build-up of frustrations and help him/her to remove self to “safe area.” Create a key word or phrase that will alert the student that it is time to go. Practice using these words/phrases when the student is calm.</li> <li>• Develop a plan and teach the student <i>what to do</i> if he/she feels angry or frustrated. Many students substitute a means of releasing this pent-up anger—long walks/ exercise, ripping paper, tearing rags, popping packaging bubbles.</li> <li>• <i>Don’t try reasoning when student is out of control. Limit discussion.</i></li> <li>• Have a plan in place if student becomes more violent. Safety for all is a priority. Consistency in approach is imperative.</li> </ul> |

### *Food-Related Behaviors and Dietary Restrictions*

For people with PWS, the message of fullness never reaches the brain—they are always hungry. In addition to this craving for food, food is metabolized at such a slow rate that it causes extraordinary weight gain. Food must be monitored and the individual supervised at all times.

- Provide positive closure. Don't hold a grudge.
- If using consequences, they should be immediate and help the youngster/adult learn from the outburst—e.g., saying "I'm sorry," sending a note to say they are sorry.
- Make sure access to food is restricted. This may require locked pantries, refrigerators, kitchen doors, and garbage cans.
- Educate and inform *all family members, neighbors, and friends* regarding the restricted dietary needs.
- Be aware of the many "tricks" the person may develop to get extra food beyond that dictated by his/her diet, and be alert for the many clever hiding places he/she may develop to store "illicit" food items.
- Supervise in kitchen, dining room, and in all food-related areas.
- Avoid providing the youngster or adult with money beyond that for a singular item for which he/she may be shopping (under supervision). Lock up all sources of money, including purses. Money buys food!
- Address any stealing or trading of food in private.
- Provide guidelines to school for treats or eating of extra food. Communication with all in school is very important.
- Follow calorie-controlled diet. If a special calorie diet is needed and served by the school, a prescription must be obtained from a health care provider and should be a part of the student's educational plan.
- Provide positive closure. Don't hold a grudge.
- If using consequences, they should be immediate and help the student learn from the outburst—e.g., saying "I'm sorry," sending a note to say they are sorry.
- Make sure lunch is placed with a bus driver and /or an assistant on the ride to school.
- Educate and inform *all people* working with this student, including bus drivers, custodians, secretaries, and volunteers.
- If the student states he/she has not had breakfast, call parents or caregiver before giving more food. (Oftentimes they say this to get more food.)
- Supervise in lunchroom and in all food-related areas—including vending machine areas. In some cases, student may need to eat in classroom (with peer/friend).
- Many require supervision in hallways or near unlocked lockers at all times.
- Avoid allowing the student to have money. Lock up all sources of money, including purses. Money buys food!
- Address any stealing or trading of food in private.
- Follow guidelines for treats or eating of extra food. Communication with home is very important.
- Follow calorie-controlled diet. If a special calorie diet is needed and served by the school, a prescription must be obtained from a health care provider and should be a part of the student's educational plan.

*(Continued)*

Table 12.4. Behavior Management Strategies for Home and School (*Continued*)

| Common Behavior Characteristics in Youngsters and Adults with PWS                                                                                                                         | Possible Management Strategies                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
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|                                                                                                                                                                                           | Home                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | School                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
| <i>Food-Related Behaviors and Dietary Restrictions—continued</i>                                                                                                                          | <ul style="list-style-type: none"> <li>• Don't delay snack or lunch; if this is necessary discuss ahead.</li> <li>• Limit availability and visibility of food. Be aware of candy dishes and other sources of food.</li> <li>• Praise situations where student does not take food when you see they could have.</li> <li>• Avoid using food as a reward or incentive.</li> <li>• Be aware of smells—there is nothing like the smell of popcorn to make a person with PWS agitated.</li> <li>• When going on a family outing, discuss all food-related issues <i>ahead of time</i>. Will you bring snack along or will it be purchased? If purchased, what will it be? Will the outing interfere with the time of a meal or snack? Provide supervision at large family get-togethers so that difficulties are avoided.</li> <li>• Obtain weekly weight if indicated.</li> <li>• Daily exercise should be a part of student's schedule.</li> </ul> | <ul style="list-style-type: none"> <li>• Don't delay snack or lunch; if this is necessary discuss ahead.</li> <li>• Limit availability and visibility of food. Be aware of candy dishes and other sources of food.</li> <li>• Praise situations where student does not take food when you see they could have.</li> <li>• Avoid using food as a reward or incentive.</li> <li>• Be aware of smells—there is nothing like the smell of popcorn to make a student with PWS agitated.</li> <li>• When going on a field trip or other outing, discuss all food-related issues <i>ahead of time</i>. Will you bring snack along or will it be purchased? If purchased, what will it be? Will the outing interfere with the time of a meal or snack?</li> <li>• Obtain weekly weight by school nurse if indicated.</li> <li>• Daily exercise should be a part of student's schedule.</li> </ul> |
| <p><i>Poor Stamina</i></p> <p>People with PWS tire more easily and may fall asleep during the day. Morning is typically their optimal performance time, when energy level is highest.</p> | <ul style="list-style-type: none"> <li>• Get person up and moving. Send on errand. Take a walk.</li> <li>• Schedule high energy, mobilizing activity after lunch.</li> <li>• Offer items/activities which stimulate large muscles and deep breathing—balloon blowing, party blowers.</li> <li>• Provide scheduled rest time or a quieter activity if needed.</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | <ul style="list-style-type: none"> <li>• Get person up and moving. Send on errand. Take a walk.</li> <li>• Schedule high energy, mobilizing activity after lunch.</li> <li>• Offer items /activities which stimulate large muscles and deep breathing—balloon blowing, party blowers.</li> <li>• Provide scheduled rest time or a quieter activity if needed.</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |

### *Scratching and Skin Picking*

These two behaviors are often seen in individuals with PWS and may be worse during times of stress or boredom. Combined with a higher pain threshold, these behaviors can result in tissue damage if not controlled.

- Use diversion—provide activities to keep hands busy (coloring, computer time, play dough, hand-held games).
- Keep nails short. Apply lotion liberally—it keeps skin slippery. Skin that is soft and moisturized is more difficult to pick. Applying lotion can also be an effective diversion.
- Provide supervision. Reward and praise for not picking.
- Cover area with bandage or similar covering.
- Don't just tell him/her to stop picking—it won't work.
- Apply mosquito repellent before any walks or outside activity.

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- Apply mosquito repellent before any walks or outside activity.

### *Difficulty with Peer and Other Social Interactions*

While people with PWS want, need, and value friends, they often have difficulty with social interactions. It may also be difficult for them to be exposed to the unpredictability of others for long periods. The need for order often translates into fairness issues and comparing themselves to others, often resulting in anger.

- Many do better in small groups and at times alone.
- Pre-plan outings. Keep time short.
- Provide "supported" social outings, planned activities with a friend.
- Include child in planning activities that are of interest to him/her (board games, puzzles, computer games).
- Provide social skills classes that emphasize sharing, taking turns.

- Many do better in small groups and at times alone.
- Pre-plan outings. Keep time short.
- Provide "supported" recess or social outings, planned activities with a friend.
- Include child in planning activities that are of interest to him/her (board games, puzzles, computer games).
- Provide social skills classes that emphasize sharing, taking turns.

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*Source:* Adapted with permission from "Information for School Staff: Supporting the Student Who Has Prader-Willi Syndrome," compiled by Barbara Dorn and available from the Prader-Willi Syndrome Association (USA).



sense when viewed both from a methodological framework and historically. Methodologically, the “gold standard” of drug studies is the two-group, treated versus control, procedure. This procedure is even more robust if both the patient and the clinician are “blind” as to who receives the medication and who receives the “placebo.” However, to conduct such studies requires a medication with a strong indication of effectiveness and a sufficiently large population in which to conduct the study. To date, no medication has met the “strong indication” criterion in those with PWS. Secondly, the size of the patient population, even at the largest PWS centers, is quite small (80 to 120), so that obtaining a sufficiently large treatment and control group is difficult. Thirdly, not all affected individuals need medication; among those who do, not all need the same drug. Some may need a medication for anxiety while others need an antidepressant, further narrowing the size of the eligible research population. Finally, when a person is in sufficient behavioral crisis to require medication, the ethics of assigning them to a “placebo” control group is questionable. Some studies can compare two separate medications for the same disorder, such as two separate antidepressants, but again the overall size of the eligible population at any one center makes such studies extremely difficult.

There are also historical reasons for the lack of studies in this area. Following the original description of the syndrome, many affected individuals were treated both with standard appetite-suppressing medications and with “routine” mood and behavior-altering medications. Subsequently, the use of these medications was discontinued after early therapeutic trials with appetite-suppressing agents, thyroid supplements, diuretics, and psychotropic agents proved unsatisfactory.<sup>7</sup> Additionally, many psychotropic agents increase appetite, while others suppress cognitive capacities, so that, frequently, the use of medications *worsens* behaviors rather than helping. Indeed, following a small study in 1992, Tu et al. declared, “it is becoming increasingly clear that the use of neuroleptic and appetite suppressive medications in PWS is undesirable.”<sup>61</sup> Subsequent efforts to find a reliable, appetite-suppressing medication have been, and remain, unsuccessful.<sup>52</sup>

Despite this gloomy report, there emerged several case reports suggesting positive behavioral effects with fluoxetine.<sup>3,18,63</sup> At the same time, a three-wave survey study of 106 persons with Prader-Willi syndrome, conducted between 1989 and 1995, and a separately sampled cohort in 1998 indicated that, at some point in time, most psychotropic medications had been employed for behavioral difficulties, either singly or in combination, with little success.<sup>32,67,68</sup> These studies indicated three medications that reliably modified behavior: haloperidol, thioridazine, and (with some variability) those medications termed selective serotonin reuptake inhibitors (SSRIs), of which fluoxetine was the prototype. Subsequent reports, however, indicate that SSRIs are neither universally effective, nor without side effects, including increased appetite.<sup>43</sup>

The last decade has seen the advent of several “new generation” medications. These have prompted renewed interest in studying medication impact in this population, as evidenced by several recent reports. Positive behavioral effects are reported for seven patients with PWS

treated with risperidone.<sup>22</sup> Others, however, report serious side effects from this same medication.<sup>51</sup> Similarly, in two studies totaling 13 patients, 12 had mildly improved mood and some reduction in skin picking with topiramate, a new antiepileptic medication.<sup>53,56</sup> In the latter study, however, 4 of the 7 patients were also on other medications, primarily SSRIs. In addition, while several patients had a modest improvement in the amount and severity of skin picking, one displayed markedly worsened picking behaviors and initiated hair pulling, requiring additional medication for this behavior. Further reports suggest that the use of these medications must be approached with extreme caution, as a number of serious side effects have been reported (see Chapter 17).

Thus, it appears that the medication picture is not as bleak as that described by Tu<sup>61</sup> only a decade ago. A range of effective medications is currently available. However, as in the general population, some patients respond well to one medication and not to another, so trials of several medications may be necessary. And, while sparse, the available data do suggest some cautions to consider when prescribing for this population. These cautions are both physiologic and behavioral.

First, due to an altered body composition and metabolism, persons with Prader-Willi syndrome often have extremely idiosyncratic, frequently unpredictable, and often negative responses to medications. Additionally, many demonstrate much lower dose thresholds and tolerances and longer drug half-lives than those of a nonaffected population.<sup>9</sup> Further, symptom response may be evident much sooner than in other populations. It is not unusual to observe improvement with SSRI therapy in as little as 24 hours, particularly in the area of improved flexibility and reduced irritability. This rapidity of response has led to speculation that the effect may be nonspecific rather than as a classical antidepressant agent. Finally, side effects may be different, more intense, and longer lasting than in other populations.

An additional caution concerning the use of medication concerns the meaning of behavior. As has been described, many difficult behaviors are commonly present in the behavioral phenotype of persons with PWS, behaviors that often become exaggerated in frequency or severity with stress or physical illness. Many parents report feeling pressured to medicate their child when behaviors become exaggerated in response to stress, rather than altering the environment to manage the stress. For instance, the person unaffected by Prader-Willi syndrome facing the normal stress and grief that accompanies the loss of a parent experiences a long period of sadness often accompanied by irritability, depressed levels of performance, and withdrawing from social interactions. For most, time and “just getting through it” is the recommended treatment. Too frequently, a similar period of accommodation is denied the person with PWS under similar stress, as the change in behavior is ascribed to a deterioration of brain mechanisms associated with PWS rather than recognizing that the person with PWS may have a more intense and prolonged, yet normal, reaction to the stress of grief. Many parents report feeling that the rush to medication is for the convenience of the service provider (e.g., group home staff, teacher) rather than

the needs of the person with PWS. Multiple experiences of this sort render many parents reluctant to consider medication, even when it is appropriate. Thus the use of these medications remains a tool that must be employed with great caution.

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# Inpatient Crisis Intervention for Persons with Prader-Willi Syndrome

Linda M. Gourash, James E. Hanchett,<sup>†</sup> and Janice L. Forster

*Editor's comment: The authors have summarized their clinical experience in caring for several hundred persons with Prader-Willi syndrome (PWS) who were hospitalized for crisis intervention. It is emphasized that this experience was with a referral population in crisis and does not reflect the population of persons with PWS in general. Crises in persons with PWS appear to be most often associated with extrinsic factors.*

Inpatient care of persons with PWS has afforded a unique opportunity to obtain detailed historical information, to review extensive medical records including prior hospitalizations, and to observe firsthand and in depth the complex phenomenology of PWS. While clear patterns of PWS crisis have emerged and are described here, the interventions and recommendations are far more variable and must be individualized based on each patient's unique personality and circumstances. Inpatient hospitalization is at times the only way to evaluate in adequate detail the circumstances leading to crisis in PWS and to identify or create the resources necessary for crisis resolution.

At the time that this work was done at The Children's Institute of Pittsburgh, Pa., the clinical leadership consisted of a developmental pediatrician who functioned as attending physician and team leader, a developmental neuropsychiatrist, an internist (nephrologist), a head nurse, a psychologist, and case manager(s). There was an integrated collaboration of these disciplines meeting as often as three times per week in addition to a more typical patient-centered staffing model, which included other rehabilitation disciplines such as physical therapy, speech and language therapy, and occupational therapy.

Extended hospitalization (usually 1 to 6 months in duration) provided a unique venue to evaluate treatment interventions in situ. Outpatient follow-up through office visits, telephone, and e-mail communications enabled the clinical evaluation of treatment results across time for a large number of patients manifesting the more severe problems associated with PWS.

Crisis intervention requires involvement in complex scenarios and problems that do not lend themselves easily to systematic investigation. The relative contribution of patient factors and environmental factors leading to crisis is

<sup>†</sup> Deceased.

*an area worthy of study. The authors offer their experience as an aid for clinicians addressing these complex problems perhaps for the first time and for researchers who may choose to investigate the sources and resolution of crises in individuals with PWS.*

## The Nature of Crisis in Prader-Willi Syndrome

Crises in persons with Prader-Willi syndrome (PWS) involve deterioration in level of functioning across medical, behavioral, and/or psychiatric domains, or in the person's support system. Crises most often appear to be the result of extrinsic factors interacting with the typical features of PWS, while a smaller number of cases appear to involve the more severe behavioral spectrum of the disorder or frank psychiatric illness. Usually several areas of deterioration must be addressed simultaneously in order to stabilize the patient. Frequently outpatient interventions may not be comprehensive or sufficiently intensive to effect a sustained improvement.

A crisis for an individual with Prader-Willi syndrome may be abrupt or, as often occurs, the culmination of multiple contributory events. Because of the unique and complex problems associated with PWS, these situations may benefit from a specialized approach implemented by a multidisciplinary team experienced with the disorder.

The goals of crisis intervention include the following:

- Reversal of medical, psychiatric, or behavioral deterioration
- Restoration of an existing support system or prevention of breakdown in a potentially overwhelmed system
- Development of a realistic and comprehensive post-hospitalization plan that supports the above goals for the foreseeable future

## Reasons for Referral

### Medical Crises

Medical crises in persons with PWS stem primarily from the consequences of a fundamental disorder of satiety.<sup>21</sup> Rarely, stomach rupture from overeating has occurred (see Chapter 6). More often there is an unrelenting weight gain leading to morbid obesity. Persons with Prader-Willi syndrome usually have *exceptionally low caloric needs*, resulting from decreased muscle mass and physical activity, as well as varying degrees of excessive food-seeking behavior. The latter is sometimes extraordinary. Overestimates of actual caloric needs by caretakers and professionals can add to the problem. Persons with Prader-Willi syndrome are at risk for sleep-disordered breathing (SDB)<sup>14,15,19,20,30,33</sup> (see discussion in Chapter 5). Clinical experience also indicates that obese persons with PWS and a body mass index (BMI) greater than 35 appear to be at increased risk for complications resulting from SDB (BMI = weight in kg/height in meters<sup>2</sup>). These breathing abnormalities, if untreated, can eventually lead to obesity hypoventilation and right heart failure (*cor pulmonale*), which may first present as sudden critical

illness, prolonged hospitalizations, chronic disability, and sometimes death. Children appear to tolerate obesity less well than adolescents and adults; persons of all ages, including young children with Prader-Willi syndrome, can die of obesity-related complications.

### **Food-Related Behavioral Crises**

Food-seeking behavior may include foraging for food in and out of the home and consuming spoiled, raw, frozen, or otherwise inedible foods. Older children and adults may steal food or money or use their own money to buy additional food. They may “phone out” for food, elope in search of a restaurant, or enter a stranger’s home to seek food. Persons with PWS may pick and break locks or steal keys to enter a locked kitchen. They may display violent outbursts or aggression related to food acquisition or to attempts to set appropriate limits. The more success/notoriety they experience, the more persistent they are in attempting to obtain additional food. In some cases, once this process has begun, the more families attempt to intervene and the more persons with PWS may exhibit behaviors that become intolerable. Families often find themselves in a situation that is spiraling out of control. Law enforcement may become involved, further complicating management.

### **Behavioral and Psychiatric Crises**

Individuals with PWS appear to be more vulnerable to stress. Cognitive deficits (specific learning disabilities) often diminish their ability to adapt to change. Persons with PWS are exceptionally dependent on others to provide structure and control of their environment. Transitional periods such as family moves, changing schools, or moving from school to work environments can all result in a loss of structure and consistency. Limited coping mechanisms may result in extreme maladaptive behaviors that are uncommon in persons without PWS. Dangerous, aggressive, destructive, disruptive, and otherwise intolerable behaviors are sometimes symptoms of psychiatric illness. Self-endangerment, self-mutilation, and rectal-picking can all result in additional medical complications. Stress appears to be a contributing factor in the onset of major psychiatric disorders such as adjustment disorders, anxiety disorders, mood disorders, psychoses, and impulse-control disorders such as intermittent explosive disorder. Accurate psychiatric assessment and diagnosis is greatly aided by a familiarity with the common personality features of the syndrome, including the propensity of persons with PWS to engage in manipulation and falsification of facts.

### **Medical Problems Requiring Intervention**

*Editor’s note: Selected medical terms are defined in the Glossary at the end of this chapter.*

### Morbid Obesity

Morbid obesity is defined as a degree of excess body fat that is associated with a high risk for obesity-related complications. In the general adult population, a BMI of 40, or 200% of ideal body weight is often used as a boundary for defining morbid obesity, although obesity-associated morbidities certainly occur at lower levels of BMI. In PWS, the additional factors of substantially reduced lean body mass at any given level of BMI, inactivity, and behavioral characteristics may further exacerbate or interfere with the management of some types of obesity-related morbidities. Such morbidities include the following:

- Sleep-disordered breathing, hypoventilation, pulmonary hypertension and cor pulmonale
- Leg edema, skin breakdown, cellulitis, and venous stasis disease with risk for thrombotic events
- Type 2 diabetes and associated complications
- Hypertension
- Intertrigo (skin breakdown, yeast and bacterial infections in deep fat folds)

### Obesity Hypoventilation and Cor Pulmonale

Disordered breathing and respiratory compromise are the most commonly encountered PWS-associated medical crisis requiring inpatient management. Virtually every kind of sleep-disordered breathing has been described in persons with PWS,<sup>13,19,20,32,33,36,37</sup> including individuals who do not meet BMI criteria for obesity. In our experience, morbidly obese persons with PWS at any age may be particularly susceptible to nocturnal hypoxia and edema. The onset may be rapid or slow. In some patients, especially the young, respiratory failure can develop quickly in a situation of steadily worsening obesity. More typically, gradually increasing weight is accompanied by decreasing stamina, reduced activity, and the insidious onset of cardiopulmonary abnormalities. In older persons, long-standing mild obesity can result in chronic dependent edema and venous and lymphatic damage. Recognition is aided by a high index of suspicion for sleep-disordered breathing in obese patients.

Koenig<sup>25</sup> describes the clinical picture of hypoventilation in obese persons as oxyhemoglobin desaturation in the absence of abnormalities in the pattern of breathing. Hypoventilation is characterized by “constant or slowly diminishing oxyhemoglobin desaturation without the cyclic, episodic or repetitive changes in oxygen saturation associated with apneas and hypopneas or the arousal that terminates these abnormal breathing events.” This sustained hypoxia can be seen on sleep pulse oximetry and is the typical pattern that we have observed in obese patients with PWS, but is relatively uncommon in non-PWS obese persons.<sup>25,38</sup> Hypoxia has long been known to cause increased pulmonary vascular resistance which, over time, leads to right heart overload.<sup>10</sup>

In PWS, cardiomegaly on chest radiograph (Figure 17.1) is a late finding in the course of obesity hypoventilation and may indicate right heart failure. In these patients, the right ventricular failure (cor pulmonale) of obesity hypoventilation usually occurs in the presence of healthy, *asymptomatic* lungs. Even when daytime and nighttime hypoxemia is profound, there may be wheezing in some, but frank pulmonary edema is usually absent and the left ventricle is generally healthy. Diagnostic modalities that are clinically useful in identifying left heart failure are less helpful in this condition. Right ventriculomegaly or evidence of increased pulmonary artery pressures on echocardiography depend on a good view of the right ventricle, which is often difficult to obtain in a very obese person.

The clinical picture of cor pulmonale is of shortness of breath, worsening daytime sleepiness, leg swelling and cardiomegaly. Unrecognized right heart failure undoubtedly contributes to some cases of sudden death, pneumonia, and reactive airway disease in obese patients with PWS. Healthy persons with PWS sometimes have a low normal hematocrit of 33% and a hemoglobin of 11g per dl. For those with obesity hypoventilation and whose hematocrit and hemoglobin usually fall in the low normal range, levels of 36% and 12 g per dl or greater, respectively, may represent an elevation in response to hypoxia. The usual carbon dioxide (CO<sub>2</sub>) combining power is 25 mmol/L or less, but in those with early CO<sub>2</sub> retention it is 29 mmol/L or higher. These subtle changes may help identify individuals at significant risk for CO<sub>2</sub> narcosis if given amounts of supplemental oxygen (O<sub>2</sub>) sufficient to normalize oxygen saturations. Overuse of oxygen causing iatrogenic CO<sub>2</sub> narcosis has led to intubation and admission to critical care with consequent deconditioning, markedly worsening and prolonging this crisis. Recovery and reconditioning become especially difficult if a tracheotomy is performed in a PWS-affected person.

The physiology of obesity hypoventilation syndrome (OHS) has not been fully illuminated.<sup>4,25</sup> Many variables have been studied in compar-



**Figure 17.1.** A young patient (shown in Figure 17.4) had cardiomegaly on radiograph (left), which resolved to normal heart size (right) after 5 months of rehabilitation. Normalization of pulmonary hypertension was demonstrated by echocardiogram shortly afterwards.

ing persons with OHS with obese persons who do not develop OHS. One common finding appears to be that persons with OHS ultimately develop reduced lung volume.<sup>3,22</sup> It is not clear why some obese persons (non-PWS) develop the disorder and others do not,<sup>31,34</sup> implying multiple mechanisms.<sup>4</sup> It is likely due to a combination of factors causing hypoventilation including congenitally decreased musculature,<sup>24,35</sup> increased work of breathing due to decreased chest wall compliance and, in some cases, partially obstructed airway anatomy.<sup>32</sup> There is some evidence for decreased central or peripheral ventilatory response to hypoxia and hypercapnia,<sup>2,28</sup> an abnormality also reported in non-PWS persons with obesity-hypoventilation.<sup>27,31,39</sup> Other factors may exist. Obstructive hypopneas or apnea during sleep may be present but are clearly not necessary.<sup>4,24</sup>

The late stages of obesity-hypoventilation have been termed “Pickwickian syndrome”<sup>8</sup> after the boy “Joe” who appears in Chapter 4 of Charles Dickens’ *The Pickwick Papers*. Numerous authors have suggested that Joe was modeled on a child with Prader-Willi syndrome. Despite its historical and literary interest, the term is best avoided as it has confused parents and other caretakers by suggesting that the patient has acquired yet another “PW” syndrome.

### *Clinical Presentation*

The clinical presentation of OHS in PWS has been delineated from a large number of patients with PWS cared for by the authors with various degrees of hypoventilation and right heart failure. The sequence of events leading to morbidity, disability, and critical illness from obesity hypoventilation is fairly typical and can be observed in reverse during rehabilitation. The sequence can develop over a period of months in the face of rapid weight gain and severe SDB or slowly in patients whose weight has been more stable but in the obese range for many years:

- Stage 1—asymptomatic nocturnal hypoxia (detectable only by pulse oximetry study during sleep)
- Stage 2—fluid retention (clinical edema, nonpitting increase in tissue turgor); decreased endurance
- Stage 3—daytime hypoventilation and hypoxia; edema may be massive
- Stage 4—respiratory failure, which may be subtle or brought on suddenly by illness or overuse of oxygen therapy

*Stage 1. Nocturnal Hypoventilation and Hypoxia:* A maximum “safe” weight for obese persons with PWS has not been defined but, based on our experience, appears to be something less than 200% of IBW (ideal body weight) based on the 50th percentile weight for height. Hypoxia first appears during REM phases of sleep.<sup>19</sup> This finding is subclinical and not evident unless detected by specific testing with pulse oximetry. Full sleep studies are needed to recognize obstructive and apneic events, however. Not every sleep lab is aware that significant hypoxia may occur in the absence of apneas and arousals.



*Stage 2. Fluid Retention:* In the PWS population, edema often is the earliest clinical sign of obesity-hypoventilation in this population; *it is frequently missed*. The reason for this appears to be the visual subtlety of edema in the obese child or adult. One useful way to describe this type of edema is that “the fat gets hard” as the turgor (firmness) of dependent tissues increases. In our experience, *pitting is usually absent*. Manual comparison (not compression) of tissue in the lower part of the body to the upper extremities will demonstrate an increased density of the tissue in the lower part of the body to the level of the knees, thighs, hips, waist, or higher. This finding is not always appreciable in children. In the absence of diuretic use, the level of edema correlates fairly well with the severity of hypoxia. Therefore detection of a lesser degree of edema to the knees or thighs is especially valuable as an early sign of increased pulmonary artery pressures. These patients typically have normal resting oxygen saturations during the day but pulse oximetry testing during exercise will sometimes demonstrate desaturation. In the presence of *any* recognizable edema, nocturnal oxygen desaturations are usually quite extensive, especially in children and adolescents, and may be present throughout the night without arousals (Figure 17.2).

Decreased exercise tolerance can also be a sign of obesity hypoventilation. However, decreased tolerance is difficult to differentiate from the noncompliance with exercise often displayed by persons with the syndrome. Families do not always perceive the symptom because young children are adept at appearing to carry out their usual activities while conserving their energy. Similarly, orthopnea (sleeping with extra pillows or sitting up) and symptoms of OSA (obstructive sleep apnea) are only sometimes present. Rapid weight gain in an individual with PWS that is not explained by increased access to food may also be a sign of fluid retention.

*Stage 3. Daytime Hypoxemia, Clinical Cardiopulmonary Compromise:* Even in this late stage, obese patients with PWS sometimes come to medical attention with only complaints of reduced exercise tolerance. Ambulatory patients with daytime oxygen desaturations often have edema (nonpitting) to or above the level of the thighs and hips. Extensive nonpitting edema to the level of the chest can still be subtle enough to be missed (Figure 17.3), but other patients visibly display massive edema, especially in the lower extremities, causing secondary morbidity: weeping sores, cellulitis, and most ominously, impaired ambulation. Some patients are quite sedentary and increased daytime sleeping may be a prominent symptom. Inactivity further impairs the quality of ventilation both during the day and at night. Oxygen saturations when the patient is awake and sitting quietly may be well below 85%, dropping still lower with activity. Cardiomegaly on chest X-ray sometimes still appears “mild.” As persons reach the stage of daytime hypoxemia, they will typically increase their resting respiratory rate, but this tachypnea >25/min is not readily appreciated since it is not accompanied by a visible increase in respiratory effort. At rest the tidal volume is small.<sup>31</sup> Resting breath sounds are often barely audible with the stethoscope.

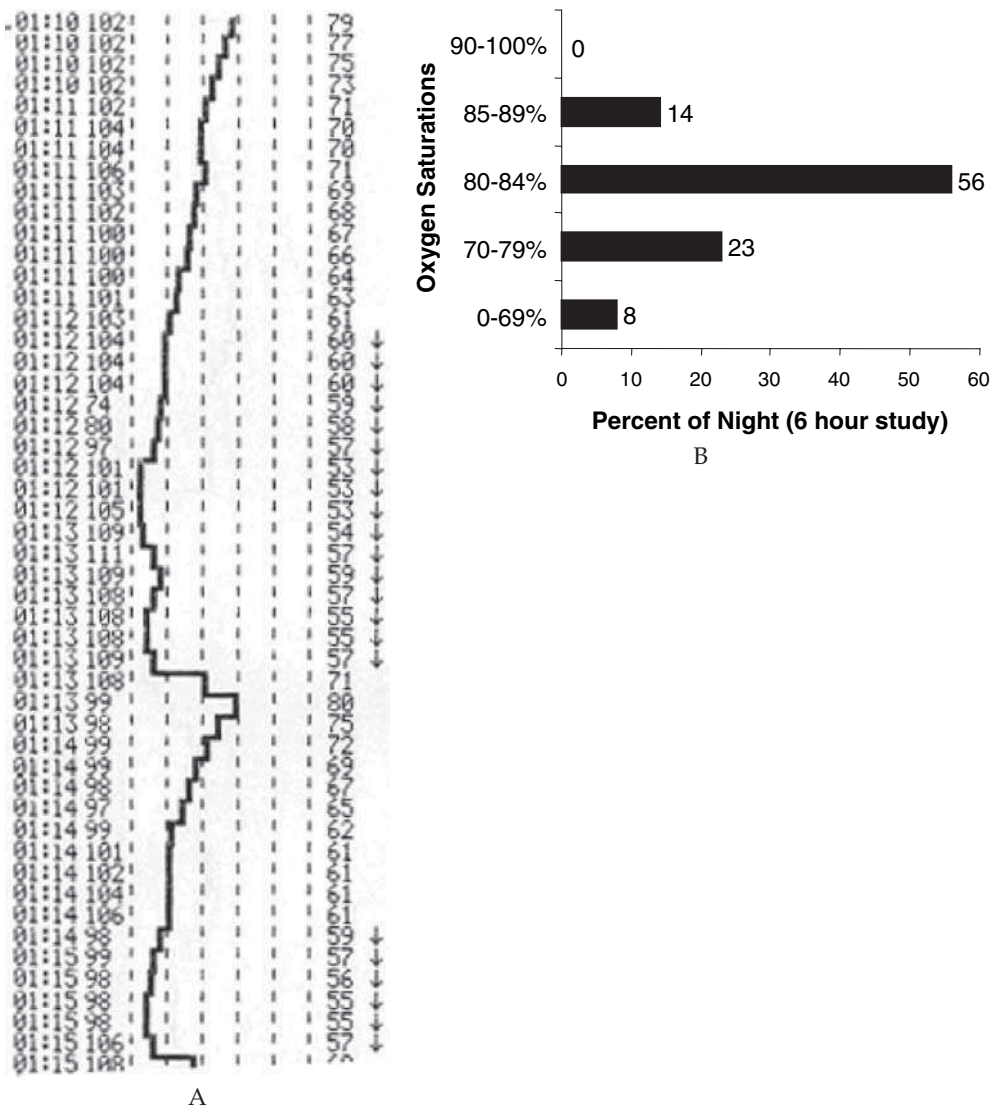


**Figure 17.2.** A. Pulse oximetry studies during sleep are very useful in identifying low blood oxygen in obese patients with PWS. These studies are relatively inexpensive and may be arranged at home while waiting for a formal sleep study. This 5-minute sample from a 6-hour study shows the severe hypoxia with oxygen saturation dipping below 60% (normal 93%–96%), which took place in a severely obese teenager who was only slightly symptomatic. She had mild shortness of breath with exertion and a subtle increase in tissue turgor of her lower body (fluid retention from early right heart failure). B. The bar graph depicts the data from a 6-hour night time study of the same teenager. The graph shows that once asleep she spent the entire night with oxygen saturations below 90%, most of the night (56% of the 6-hour study) with oxygen saturations in the 80%–84% range, and 8% of the time under 70% (0%–69% range). These abnormalities in oxygenation may take place without obstructive or non-obstructive sleep apnea and are primarily due to poor ventilation. Hypoxia is sometimes overlooked on sleep studies because there are no “events” in the form of apnea or arousals.

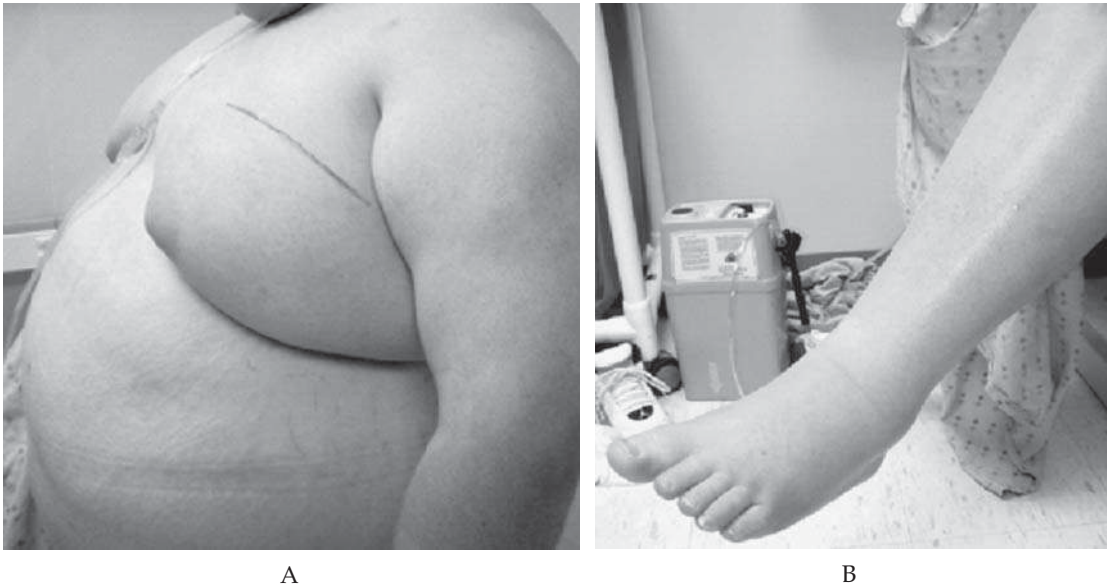


**Figure 17.3.** **A.** This young man with PWS had severe nocturnal and daytime hypoxia and palpable edema (increased tissue density) to the upper chest (marker line). **B.** Lower extremity edema may not be visually impressive (same patient) and is easily overlooked.

With activity, however, increased respiratory effort is more evident and often reported by family members as shortness of breath.

*Stage 4. Respiratory failure:* Respiratory failure with CO<sub>2</sub> retention is a life-threatening condition that may be acute or chronic. Obese persons with PWS may continue to survive in a compensated state in Stage 3 for years without evidence of respiratory failure *if* their obesity is stable and *if* they remain active. However, they will deteriorate eventually or they may suddenly become critically ill when decompensation is precipitated by an intercurrent respiratory illness or an injury resulting in decreased ambulation. Our clinical experience indicates that both inactivity and overuse of oxygen therapy may cause worsening daytime and nighttime hypoventilation with worsening CO<sub>2</sub> retention. (See Management section, below.)

We have rehabilitated a number of patients from very late and chronic obesity hypoventilation and cor pulmonale and believe that as long as a patient can be made to be ambulatory and be calorically restricted so that weight loss occurs, the condition is usually reversible. Clearly the younger the patient and the earlier the intervention, the better the prognosis for full recovery from critical illness.

### Management of Obesity Hypoventilation and Cor Pulmonale

#### *Activity and Diet*

Two primary modalities are effective in reversing the cardiopulmonary deterioration of obesity hypoventilation. These are calorie restriction and ambulation. Rehabilitation to a higher level of physical activity is

essential for recovery. Even the most seriously ill patients, if conscious, will benefit from this process immediately upon hospitalization. Patients who are critically ill, edematous, and short of breath are understandably reluctant to move. The typical Prader-Willi behavioral traits of stubbornness and manipulation may become immediately life-threatening when patients refuse to cooperate. Therefore skilled therapists working in teams of two or three may be needed to initiate activity in a nonambulatory patient (Figure 17.4).

Every effort should be made to encourage ambulation and physical activity, and patients with PWS should not be fed in bed unless absolutely required by their medical condition. Nurses and therapists will need to work together; consistent behavioral rewards and consequences should be used by the nursing and other hospital staff. Tactics may include delaying meals until modest therapy goals are achieved. Communication with the patient should take into account the personality traits typical of the syndrome to avoid nonproductive efforts. Rehabilitation consists of gradually increasing demands for physical activity beginning, if necessary, with walking a few steps to a chair for meals. Physical and occupational therapists should be given adequate support from nursing staff and adequate time to wait out the inevitable PWS



A



B

**Figure 17.4.** **A.** Nine-year-old boy with massive edema, profound hypoxia, and dangerous levels of CO<sub>2</sub> retention from obesity hypoventilation and cor pulmonale. Physical activity is an essential component of management and recovery, even in the critically ill patient. **B.** Six months after presenting in critical condition this same 9-year-old boy was active and healthy in school.



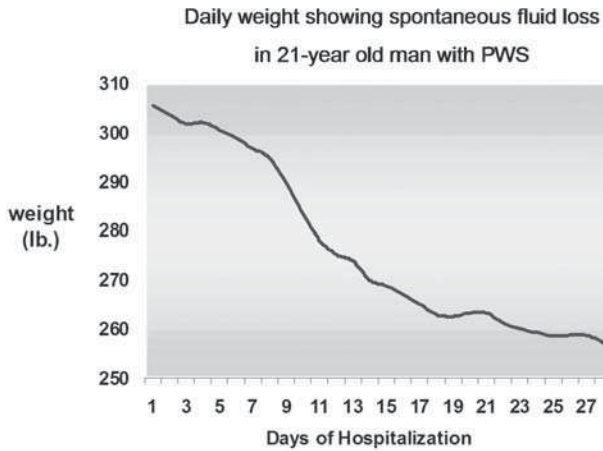


**Figure 17.5.** This graph shows the daily weight measurements of a patient (pictured in Figure 17.3), beginning at the time of his admission to a rehabilitation unit. He lost 48 pounds in his first 28 days of rehabilitation, with rapid improvement in his endurance and hypoxia. This massive fluid loss is achieved without the use of diuretic medications and appears to be a response to calorie restriction and increased physical activity, which improves ventilation.

behaviors such as whining, crying, delaying, manipulation, and frank refusals. Additional behavioral incentives also may be required. A crisis intervention team approach can help to facilitate this process.

Our experience is that a daily intake of 600–800kcal provides adequate early nutritional maintenance in the obese, ill patient with PWS. Higher caloric intake is not needed, even for healing of self-injury wounds or decubiti (bedsores). The reader is referred to Chapter 6 for additional discussion of diet and nutrition in PWS.

### *Spontaneous Diuresis*

Spontaneous diuresis of edema fluid and improving oxygen saturation are hallmarks of recovery. The known natriuretic effects of a low-calorie diet<sup>23,26</sup> combined with increased activity<sup>29</sup> result in a diuresis that is at times dramatic (Figure 17.5). In our experience, patients have eliminated as much as 2 liters of fluid per day without diuretics during the initial stages of rehabilitation. Half a kilogram weight loss per day is typical. In the absence of drugs that alter renal function, such as diuretics or topirimate, this rapid diuresis has not been associated with electrolyte abnormalities. The time frame for this diuresis is variable. While it is usually seen within days, in several severely affected individuals, diuresis was delayed many weeks despite early ambulation and strict diet. Further, we have observed that in this patient population, use of diuretics appears to delay this diuresis rather than assist it, even if azotemia is avoided.

### *Use and Misuse of Oxygen Therapy*

The fundamental pathophysiology of OHS should be kept in mind in order to avoid mismanagement. Patients are hypoventilating, day and

night. Underlying this condition is congenitally weak respiratory musculature. Adiposity thickens the chest wall thereby further restricting excursion (Figure 17.6), and in some cases there is additional tissue stiffness with loss of compliance brought on by edema fluid, as seen in Figure 17.3. In sum, the respiratory drive is inadequate to overcome the increased work of breathing. Oxygen therapy and inactivity worsen the condition of decreased respiratory drive.

In the edematous PWS patient, hypoxemia may be assumed to be chronic (present at least at night for months or years) and need not be corrected too quickly. It is sometimes thought that oxygen therapy used to treat a young person with hypoxemia and no lung disease can do no harm. However, our experience indicates that hypoventilation may gradually and subtly worsen over hours or days in patients with hypoxemia who are given more than 1 liter/minute of oxygen (24%). Hypoventilating patients who are deteriorating do not appear distressed; the only indications of excessive use of oxygen are dropping  $O_2$  saturations and lethargy with seemingly increased  $O_2$  “requirements” to maintain “normal” saturation. Although it may appear clinically reasonable to increase the rate of oxygen flow such action can lead to worsening  $CO_2$  retention, with worsening lethargy and potential respiratory arrest. An alternate response to this situation is to decrease the oxygen flow and get the patient up and moving. If needed, assisted external positive airway ventilation (BiPAP and CPAP) is preferable to intubation because it is more compatible with keeping the patient awake and mobile.

In our experience, patients in Stages 3 and 4 appear to benefit from 1 liter/minute of oxygen without worsening their hypoventilation, provided increased activity is also demanded of them. One liter of  $O_2$  per minute by nasal cannula may raise oxygen saturations to the high

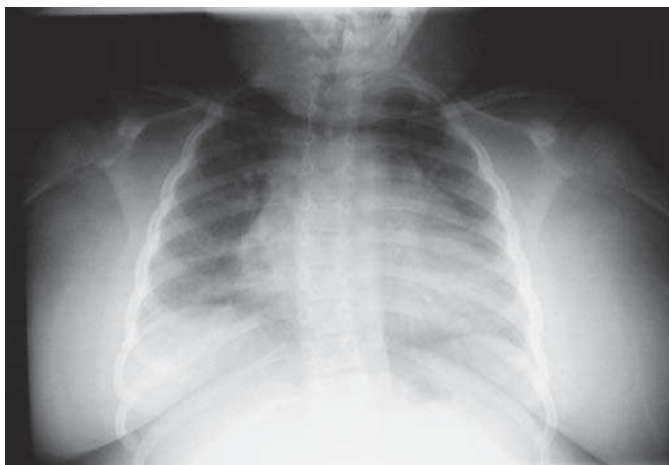


**Figure 17.6.** This chest radiograph illustrates the thickening of the chest wall in a severely obese patient with PWS. Excessive subcutaneous fat changes the energy requirements for breathing, causing hypoventilation in obese persons with the disorder.



70s or low 80s and this appears to be adequate while rehabilitation takes place. Oxygen saturations will be lower during activity, and by our observation, this is neither harmful nor does it hamper recovery. Patients should have their electrolytes checked especially if they are on oxygen therapy. After 2 to 3 days on oxygen therapy, bicarbonate levels may rise as the kidneys produce a compensatory metabolic alkalosis. This finding confirms a respiratory acidosis from CO<sub>2</sub> retention; furosemide and other diuretics may mask this effect. Unfortunately, prior to referral, some patients who refuse the BiPAP are then treated with nocturnal oxygen alone without being checked to see if their bicarbonate is rising. Prior to hospitalization, external positive airway ventilation definitely improves nocturnal ventilation in some patients, but this benefit should not be allowed to delay definitive therapy of rehabilitation and weight loss.

Many patients who initially refuse these modalities (CPAP and BiPAP) have successfully accepted these treatments with behavioral training. Sleep studies show improved ventilation and some patients report more comfortable sleep. Other patients who have completely refused therapy have also been fully rehabilitated despite ongoing profound nocturnal hypoxia. Nocturnal ventilation improves (sometimes rapidly) once rehabilitation with increased activity is underway. We do not recommend tracheostomy; the majority of persons (6 of 7 in our experience) with PWS given tracheostomies have pulled out their own tubes or otherwise endangered themselves by injuring the stoma and airway.

### *Use and Misuse of Diuretics*

If used at all, diuretics must be administered with a clear understanding of their benefits and risks. Excessive use of diuretics decreases intravascular volume with little impact on the interstitial edema of the lower body. Further, diuretic use risks the development of renal and hepatic hypoperfusion. Pulmonary edema is not characteristic of right heart failure and should not be cited as a reason to give diuretics unless left heart dysfunction has been established.

The doses of diuretics that produce azotemia also produce hepatic ischemia with rising levels of transaminase. Diuretics should be tapered and ACE inhibitors and non-steroidal anti-inflammatory drugs (NSAIDs) should be discontinued immediately. In our experience, the typical teenage and older person with PWS who has not been on growth hormone (GH) or testosterone has a serum creatinine of 0.5–0.7 mg/dl; if the creatinine is greater than 0.9 mg/dl then renal hypoperfusion/injury should be considered.

### *Positioning*

Ventilation is well known to deteriorate in the reclining position.<sup>25</sup> Very obese, edematous individuals may further compromise their own ventilation if the abdominal mass is resting on their thighs in a hospital bed. Patients benefit from sleeping in a recliner rather than a hospital bed so that their legs can be supported from below on a footstool and the abdomen can remain pendulant so as not to impinge on lung volume. These measures generally apply only to persons in Stages 3 or

4 of obesity hypoventilation. Obese persons with PWS who prefer sleeping at night in an upright position (orthopnea) can be assumed to be in danger from their obesity.

### **Obesity-Associated Conditions**

Although the following medical conditions are not inpatient crises per se, they may be commonly observed in patients with PWS who are hospitalized for medical or psychiatric problems.

#### ***Leg Edema and Cellulitis***

Leg edema in a person with PWS may accompany sleep-disordered breathing. Longstanding edema results in chronic tissue changes of the lower body including legs and lower abdomen (Figure 17.7). The result-



**Figure 17.7.** While some edematous patients retain fluid throughout their subcutaneous tissue as in Figure 17.3, others demonstrate severe leg swelling. In either case, longstanding (probably 10 or more years) and often unrecognized obesity hypoventilation results in changes in the lower extremities that are irreversible. These include dilated veins, damaged lymph vessels, and chronic stasis changes of the skin.

ing venous stasis and lymphatic damage predispose tissue to ulcers, thrombosis, and cellulitis. Intervention to prevent the prolonged condition of obesity hypoventilation is essential to avoid irreversible damage to the lymphatic and venous systems of the lower legs. There is no question that skin-picking behavior in those with PWS, while not usually resulting in infection in other parts of the body, is a major contributor to some episodes of leg cellulitis.

Direct pressure techniques to the legs or use of support hose appear to be of limited use unless they are part of a medical protocol for treatment of lymphedema. In some cases, support stockings may be counterproductive, causing tissue breakdown from pressure or constriction of fluid outflow.

Signs of cellulitis can be difficult to ascertain in the very obese individual since the legs are often already chronically swollen, indurated, and discolored. A high index of suspicion and close daily examination of the legs by caretakers seeking changes in feel or appearance is essential. Patients do not always exhibit fever or pain. Limited cases of cellulitis, diagnosed early, can be managed with oral antibiotics sometimes in combination with an antifungal agent (such as fluconazole). Preventative use of antibiotics is discouraged to prevent development of resistant strains of bacteria. However, intravenous antibiotic may be necessary in severe cases, especially if there is evidence of systemic infection. In all cases, an attempt should be made to identify the causative organism.

Maintaining and increasing physical activity and leg elevation when the patient is sitting have proven useful adjuncts in the management of these difficult conditions. Cellulitis and superficial venous thrombosis are not reasons to limit activity; rather, the reverse is true. Patients who have ceased to walk for any reason are at high risk for thromboembolic events and prophylactic anticoagulation should be considered. Rehabilitation to some level of ambulation is the highest priority.

### ***Diabetes***

Elevated blood glucose or Type 2 diabetes, seen in 25% of adults with PWS,<sup>9</sup> is frequently indicative of excessive calorie intake. In our experience, the vast majority of patients achieve normal glycemic control without medication when exercise and diet are implemented. In patients requiring diabetes medications, increasing dose requirements may be a sign of a crisis with the patient's intake and weight given the rapid rate of weight gain possible in persons with this syndrome. Patients who are on insulin are at risk for hypoglycemia if their access to excess calories is suddenly interrupted by hospitalization or other intervention.

### ***Hypertension***

Most hypertension in PWS is directly related to obesity and requires definitive intervention with diet and exercise. As with diabetes, the need for medication usually indicates inadequate intervention for the patient's deteriorating clinical condition. In our experience, the hypertension is usually labile and resolves with adequate weight loss. The

vasodilating effects of most antihypertensives only add to the amount of accumulating edema, and in some individuals their use delays the onset of the diuresis that occurs with increasing activity and caloric restriction.

### *Intertrigo*

In the very obese individual, the deep fat folds are prone to monilial and bacterial infections with occasional severe ulceration. The physical effort required to cleanse and dry deep fat folds may be beyond the capability of a single caretaker; sometimes two persons are needed to support the adipose tissue while another person performs hygiene. Obviously this is beyond the capabilities of most families, especially if the patient is resisting care.

Management of severe intertrigo includes daily or twice-daily cleansing of nonulcerated skin using a dilute (1:3 ratio) vinegar and water spray and air-drying with a heat lamp or hair dryer. Clotrimazole or powdered nystatin applied two or more times per day is also useful, especially if there is evidence of fungal infection. On rare occasions, oral antifungal or antibiotic agents may be needed if the area of involved skin surface area is great or there is ulceration. Severe ulceration may require aggressive inpatient nursing care.

## **PWS Medical Issues Not Related to Obesity**

### *Renal Dysfunction*

There is, at present, little evidence of any kidney dysfunction directly related to PWS. Renal problems seen in this population have included obstructive uropathy of congenital origin, glomerulonephritis post-infection, “diabetic nephropathy” (i.e., persons with longstanding hyperglycemia and elevated glycohemoglobin levels but without the retinopathy), renal tubular acidosis from psychotropic medication (topiramate) and Syndrome of Inappropriate Antidiuretic Hormone (SIADH) with hyponatremia from psychotropic medications, especially oxcarbazepine and carbamazepine (Trileptal and Tegretol), but also from selective serotonin reuptake inhibitors (SSRIs). Patients have developed azotemia from the volume depletion of aggressive diuretic use that at times may be greater than 70mg/dl without postural symptoms. Renal biopsy has been rarely attempted, possibly due to concerns about both patient cooperation and massive overlying fat. Persons with PWS who have not had GH treatment have a low serum creatinine due to low muscle mass. For these patients creatinine of 0.9 to 1.0 should be considered abnormal in this syndrome where typical values are 0.5–0.7.

### *Skin Picking*

The “skin picking” behavior of PWS has a wide range of severity from patient to patient and may vary in the same patient over time.<sup>17</sup> Some patients have occasional minor skin picking while others maintain large open wounds.

Skin picking is an activity that goes on continuously, intermittently, or clandestinely when the patient is calm; typical skin picking in an

individual with PWS does not appear to be an expression of emotional distress. It has been related to boredom and anxiety but objective evidence for this is difficult to establish. No specific intervention has been uniformly effective. In some cases extremely frequent picking behavior itself interferes with the patient's other activities. Severe disfigurement, recurrent infection, and anemia are reasons to consider more intense efforts to modify the behavior with hospitalization or a medication trial.

The behavior often is extinguished, at least temporarily, if healing of the wound(s) is achieved. There has been limited success using protective dressings and an intense program of alternative activity until wound healing occurs. Some wounds have healed with frequent application of an antibacterial ointment, which functions as a lubricant and interferes with picking.

Behavioral interventions targeted at the activity itself are difficult to implement. Some parents have reported success by attaching a major reward to the healing of a lesion. This approach is compatible with the basic principle that no attention, positive or negative, should be paid to the behavior itself other than to require the patient to observe social conventions and good hygiene. Spontaneously or in search of a reward, patients may cease the behavior or substitute another area of skin to pick. In rare cases, primary reinforcers have been used effectively.

### *Self-Mutilation*

Sudden self-injury or self-mutilation, with or without an emotional outburst, is a different phenomenon representing more serious pathology. Self-mutilation does not differ from skin picking in severity of the wound but in the circumstances under which it is inflicted. The actual injury may be mild (hitting self in the head) or severe (gouging a deep wound with a pen, knife, or fingers). The patient may verbalize distress, anger, self-hatred ("I'm so stupid!") or appear to be in a dissociative state. Psychiatric assessment and treatment of underlying conditions is indicated. Some patients have reported auditory hallucinations as triggers for these behaviors.

### *Rectal Self-Injury*

Rectal self-injury is a problematic behavior occurring in some persons with Prader-Willi syndrome. The behavior is not well understood. Fortunately it becomes serious in only a small number of persons with PWS. This includes patients with frequent rectal digging/injury that results in medical problems such as bleeding, infection, or fecal incontinence.<sup>5</sup>

We have made the following observations with respect to this behavior in individuals with PWS:

1. Indirect evidence of the behavior can aid in the diagnosis of unexplained medical symptoms, even if the behavior has never been observed.
  - Excessive time spent in the bathroom (a PWS trait without rectal picking)

- Feces or bloody smears on hands, toilet, fixtures, shower, bath tub, or bed linens
  - Bowel incontinence, urgency, or diarrhea (due to reflex bowel emptying following rectal stimulation)
  - Rectal bleeding
2. Anemia from chronic blood loss, while rare, can be severe. Acute hemorrhage or perforation has not been reported. Chronic ulceration is well documented by endoscopy and has been misdiagnosed and treated as inflammatory bowel disease (IBD). Clinical experience in the referral population has been that all cases of rectal bleeding or ulceration have proved to be from self-trauma and not from IBD.
  3. The behavior appears to be obsessional and compulsive; however, medications targeting OCD have not been helpful.
  4. Rectal picking/digging does not appear to be a sexual behavior, nor is it a behavioral sequela of sexual abuse.
  5. Rectal picking/digging does appear to be a nonspecific stress symptom. Marked increases in the behavior have been observed in association with ongoing interpersonal conflict and punitive disciplinary approaches, as well as during episodes of psychosis and mood instability. Diminution and/or elimination of the behavior has occurred when the underlying illness or stressor is addressed effectively.

## Special Considerations

There are a number of unusual characteristics in patients with PWS. Familiarity with these issues is necessary for the clinician to respond appropriately.

### Unreliable Self-Report

*Abnormal pain awareness* and *unpredictable fever response* can lead to underreporting of pain and missed diagnoses of serious conditions that would normally be expected to produce severe pain or fever. Diagnoses of acute surgical abdominal conditions, fractures, and serious infections have been delayed due to the failure of the patient to report pain or to show a fever. Therefore, any fever or a refusal to walk (after an injury or fall) should be taken seriously, and a good clinical examination and close follow-up are indicated until serious illness or injury has been ruled out. Patients who show decreased interest in food should be considered potentially seriously ill, medically or psychiatrically. Manipulative refusal to eat has also been observed.

*Somatic complaints* are frequent among individuals with PWS who often report numerous symptoms for which objective evidence is lacking. When there is a marked discrepancy between objective findings and subjective stress, discomfort, or functional impairment, malingering should be considered. Malingering is the intentional production of false or grossly exaggerated physical or psychological symptoms motivated by external incentives.<sup>1</sup> For the individual with PWS, external incentives may include obtaining food or medication, escaping



structure in order to procure food, or avoiding demands for exercise or other tasks.

*Factitious disorder* is differentiated from malingering by the absence of external incentives. Individuals with factitious disorder need to maintain the sick role because of intrapsychic needs.<sup>1</sup> They may engage in pathological lying about their symptoms or their personal history. Sometimes for no apparent reason an individual with PWS will provide an inaccurate medical history, reporting events or procedures that never happened. Therefore clinicians should try to verify presenting symptoms and history independently.

Suggestibility is common among patients with PWS, and they may falsely endorse complaints when asked during a routine interview about symptoms of disease. The symptoms may be variable in their occurrence (present only when asked or examined). This suggestibility in persons with PWS complicates both their medical and psychiatric evaluation and management.

*Medication seeking* is prominent with some patients (usually higher-functioning individuals) and can result in massive polypharmacy for miscellaneous complaints. These are usually conditions for which objective evidence is difficult to obtain: pain, allergies, reflux disease, constipation, and urinary symptoms. Complaints of pain and requests for analgesia are common. Consequently adult patients in the referral population were frequently on an excessive number of prescription drugs and over-the-counter and topical preparations. Persons with PWS are often very attached to their medication regimens and will sometimes vigorously resist change. They sometimes request liquid medications that are sweet to the taste. Prescriptions for symptomatic relief should therefore always be time limited and dose limited. Patients with a clear pattern of medication seeking should not have unsupervised visits to a physician. Persons with the disorder cannot be allowed to dose themselves with “as needed” medications. Nondrug therapies are preferred: heat, cold, massage, sympathy, or reassurance.

On the other hand, individuals with PWS can be truthful and reliable historians. A careful interviewer takes seriously reports of abuse, serious physical symptoms, delusional thinking, or the experience of hallucinations.

### **Abnormal Temperature Regulation**

As discussed in Chapter 5, temperature dysregulation may occur more frequently in individuals with PWS, perhaps related to a defect in thermogenesis. In two well-described cases,<sup>16</sup> hypothermia began with a change in behavior followed by decreasing activity proceeding to near coma. The patients did not want to eat, did not complain of being cold, felt cool to the touch, and became ashen. Hypothermia (81°F–94°F), decreased blood pressure, bradycardia, and slow respirations were observed. Laboratory studies revealed decreased hemoglobin, low white blood cell count, decreased platelets, hyponatremia without acidosis or hyperkalemia, and elevated renal and liver function tests. All of these changes returned to normal levels over several days as the

patients were rewarmed. Sepsis was suspected but blood cultures were negative. Neuroleptics may have played a role.

Hypothermia has usually occurred when the outside temperature was cool. In our experience, some patients have repeated episodes during the winter and experience relief during the summer months, but have recurrence during the following late fall. Bray et al.<sup>7</sup> have made similar observations.

### **Hypersomnia, Daytime Sleepiness**

Abnormalities in the sleep of persons with PWS have been documented at all ages with and without obesity.<sup>11</sup> Excessive daytime sleepiness appears to be a characteristic of PWS, but excessive medication and obesity hypoventilation should be ruled out as contributing to the symptom. Some patients meet criteria for narcolepsy and benefit from appropriate medications.<sup>18</sup> In our experience, stimulant medications and modafinil have been useful in selected cases, keeping in mind the risk of mood activation in susceptible patients. It is certain that some patients use their capacity for short sleep latency as an escape-avoidance mechanism at will and can respond to behavioral incentives to stay awake in the classroom or workshop.

## **Behavioral Problems and Psychiatric Crises in PWS Requiring Intervention**

### **Stress Sensitivity**

Individuals with PWS are *stress sensitive*; they rely on the predictability, consistency, and stability of their environment. A stress response will occur if the integrity of the environment deteriorates for any reason. The stress response can be nonspecific (increase in typical PWS behaviors), specific (emergence of atypical behaviors), or outrageous (individuals with PWS who are stressed have the potential for outrageous behavior, which should not be attributed automatically to severe psychopathology). Because the individual with PWS is dependent on environmental structure, and because their problem-solving ability is limited by impaired judgment that exceeds the deficit predicted by their intellectual deficiency and/or learning disability, individuals with PWS are usually not candidates for complete independence. Their life goal is *maximal function with support*. Among the referral population, the most common cause of functional deterioration in adults with PWS has been a misunderstanding of this principle.

Caring for an individual with Prader-Willi syndrome exhausts the resources of many families. Controlling food access and dealing with other difficult behaviors is an ongoing challenge. The price tag of “keeping the peace” or “giving in” is the inadvertent reinforcement of disruptive behaviors and the spiraling pattern of obesity and its morbid complications. The mainstay of behavior management for this syndrome is an environmental buffer in the home, school, workshop, and community that prevents rather than reacts to behavioral problems. On

an inpatient unit, this environmental buffer is called the *therapeutic milieu*. Crisis intervention provides an opportunity to have an impact on both the individual and the home environment by reestablishing the structure and consistency of rules and mutual expectations needed to effectively manage the most common behavioral issues.

The basic premise of intervention acknowledges that *at no time can a person with Prader-Willi syndrome be expected to voluntarily or independently control his/her own food consumption*. Extensive experience with a referral population has demonstrated that once food access is controlled and the principles of food security are implemented, acceptance of restrictive programming is usually excellent. Appropriate social skills and compliance with an exercise program, activities of daily living, chores, and personal hygiene are all supported by the therapeutic milieu. The experience of success is built into the program; patients receive rewards for their progress, and families are rewarded by a decrease in their level of stress.

### Psychiatric Crises

Among persons with Prader-Willi syndrome the proportion who develop serious psychiatric illness requiring hospitalization is unknown. The literature is replete with case reports of serious psychiatric illness concurrent with PWS. Among the referral population, psychiatric crises are not limited to those who have severe psychiatric illness. Persons with PWS have limited coping mechanisms due to cognitive rigidity, variability in adaptive functioning and sensitivity to stress that can result in a precipitous deterioration in mental status. Sometimes precipitating events can be identified, such as life stressors associated with leaving school, failure in a workshop, change in educational or caretaking staff, or death or illness in the family. Some presenting symptoms leading to hospitalization include depression, suicidality, aggression, property destruction, elopement, increased irritability and explosiveness, hypomania, delusional thinking and hallucinations, and self-mutilation or self-endangerment. Persons with PWS are prone to a variety of mood disorders often presenting with psychotic features.<sup>6,12</sup> In addition, psychiatric illness in this population is often accompanied by a range of behaviors usually restricted to severe and chronically mentally ill persons: attempts to swallow inedible objects, severe self-mutilation, running into traffic, fecal smearing and throwing, coprophagia, rectal self-injury, psychogenic water intoxication, deliberate property destruction, hunger strikes, refusal to move, etc. Despite the seriousness of the presenting symptoms, the prognosis is quite variable: many patients stabilize in a structured, low-stress environment either with or without psychotropic medication. At the other end of the spectrum, a small number of patients have refractory symptoms despite appropriate environmental management and multiple trials of medications.

Individuals with PWS who develop serious psychiatric crises may display behaviors that are difficult to manage even in psychiatric facilities. The therapeutic milieu of most general psychiatric units is not

designed for and often does not meet the needs of persons with PWS. Subtle but significant cognitive deficits may not be recognized, and individuals with PWS may not benefit from traditional group and individual psychotherapeutic interventions. Some patients undergo weight gain because they have access to too much food. They may forage freely from other patients. Access to recreational and exercise facilities is often limited. Among the referral population, reports of weight gains of as much as 20 pounds have occurred in a matter of days during the course of a psychiatric hospitalization. Syndromal behaviors are often misunderstood as manifestations of more severe psychopathology, or they are not adequately addressed with potentially beneficial behavioral techniques.

Even in the absence of a specialized program, most patients with PWS show an immediate improvement in their behavior upon admission to a hospital. They respond to the predictable regimen. They often have no demands made on them, and they receive too much food. This response should not be interpreted as an end to the behavioral crisis.

### **A Specialized Therapeutic Milieu**

A specialized therapeutic milieu, an essential element in inpatient crisis management, is dependent upon a trained, experienced staff. *Consistency* is the gold standard; every health care worker, nurse, physician, and therapist should understand the behaviors typical of PWS and respond to their occurrence in a low-keyed manner. For example, behaviors such as screaming and verbal abuse are best ignored. All statements made to patients should be framed in a positive rather than punitive context. It is important to assure that the patient's attempts to manipulate or triangulate personnel are unsuccessful. Even house-keeping and dietary staff members can be trained so that they will not be tricked or manipulated. Important questions about length of stay, family visits, dietary orders, and disposition plans should be answered only by designated staff. Clear lines of communication with the patient, the family, and the staff are critical. Families and other caretakers should be incorporated into the milieu through training that may involve "homework." These assignments may involve observation of direct care in the hospital or the design of a daily schedule, meal plan, or behavioral contract for use in the home. Telephone contact after discharge can assist in the maintenance of structure and the ongoing monitoring of treatment goals and interventions.

The ideal inpatient treatment plan for a patient with PWS has six major components: (1) milieu management, (2) behavioral interventions, (3) psychological therapies, (4) psychotropic medication, (5) family/staff intervention, and (6) disposition/systems intervention.

#### **1. Milieu management**

Milieu management is an essential tool for the inpatient treatment of individuals with PWS. The milieu contains several components:

- Rules of conduct
- Daily schedule of activities

- Psychological food security
- Mandatory supervised exercise
- “The Day Stops Here”

*Rules of Conduct:* The rules of conduct for patients on the unit are explained and posted next to the patient’s bill of rights in the individual’s room.

*Daily Schedule of Activities:* This modality consists of a predetermined time line of activities including wake up, grooming, therapies, meal times, exercise, leisure, rest, and bedtime. It defines the *flow* of the day and establishes structure, consistency, and predictability. This timeline is best presented to the patient in a concrete form; a wall chart may be supplemented by a written schedule which the patient carries with him through the day. The planned flow of activities is continuously reinforced by the verbal prompts of staff and therapists to “check the schedule.”

It should be assumed that the patient with PWS could have difficulty with the timely completion of ADLs (activities of daily living). Some will need assistance with grooming activities depending upon the degree of obesity as well as the level of dyspraxia.

Because individuals with PWS have hypothalamic hypogonadism, their physical and emotional sexual maturation may not be age appropriate. Many of them appear to be younger than their stated age, and their gender may appear to be ambiguous because of obesity and poorly developed secondary sexual characteristics. Among our referral population, both males and females tend to be immodest, and they may require verbal reminders to maintain privacy for grooming and dressing. Also, this privacy is essential to prevent other patients who do not have PWS from making destructive comments leading to discomfort.

*Psychological Food Security:* Psychological food security is an essential component of the management of individuals with PWS; the goal is to maintain food security across all settings both in and out of the hospital. Food security is one of the most basic skills taught to the patient’s family or other caretakers.

Food security is achieved when food access is controlled to the extent that three criteria are established:

1. There is *no doubt* when, what, and how much the person with PWS will eat;
2. There is *no hope* of receiving any more; and
3. There is *no disappointment* due to false expectations.

$$\text{Food security} = \text{No doubt} + \text{No hope} + \text{No disappointment}$$

When food access is restricted, individuals with PWS require *no doubt* about their meals and snacks. Menus are planned ahead and posted; calories are controlled, but the amount of food presented can still be generous. Although the timing of the meals and snacks remains fixed,

it is not focused on the clock; it is set by the sequence of activities across the day. This concept is critical to the achievement of *flow* through the day.

The quantity of food presented aids *psychological satisfaction*. The Red, Yellow, Green Diet (see [www.amazingkids.org/](http://www.amazingkids.org/)) is an excellent meal plan that provides large quantities of “green foods” (lettuce, green beans, tomatoes, broccoli, cauliflower, peppers), moderate amounts of “yellow foods” (lean meats and complex carbohydrates such as fruits, grains, fat free dairy, mushrooms), and extremely infrequent or minimal amounts of “red foods” (high-fat, high-calorie foods such as fats, oils, most deli meats, cheeses, desserts). The food is presented with controlled access to low-calorie, fat-free seasonings and dressings as well as salt, pepper, and hot sauce. (Individual packets eliminate discussions about the quantity of these condiments.) Sugarless gum and diet beverages including Crystal Light®, coffee and tea, and diet soda are limited, and measured quantities are used as reinforcement for exercise compliance and effort.

*Mandatory Supervised Exercise:* Mandatory supervised exercise must be scheduled into the daily plan. Walking is by far the best aerobic exercise for individuals with PWS. Two different periods for exercise are scheduled through the day.

*The Day Stops Here!* This concept is *the* most effective milieu management program for hospitalized individuals with PWS. It requires 1:1 staff for implementation. If the flow of the daily schedule is interrupted by a behavioral situation (refusal, “shutdown,” or outburst), the daily schedule stops at that point until the individual has regained motivation and behavioral control to return to programming. Individuals are encouraged to return to scheduled therapies; if the therapies have ended, prescribed “make-up work” must be accomplished before moving to the next activity. *It is essential to delay meals until make-up work has been completed.* Sometimes individuals with PWS stage behavioral shutdowns that can last for as long as a full day. However, nourishment is never withheld and an alternative calorie source is provided even if the privilege to attend mealtime is lost.

## 2. Behavioral interventions

Behavioral interventions are an essential tool for a successful treatment plan. Noncontingent reinforcement (NCR) is the delivery of reinforcers independent of an individual’s response. It is a powerful tool for establishing rapport. Typical noncontingent reinforcers include talking to the individual (nonspecific topics such as orientation, daily schedule, current events, weather; specific topics such as clothing, grooming, leisure interests) and providing leisure activities (puzzles, magazines, paper, markers).

Contingent reinforcement is the delivery of reinforcers dependent upon the individual’s response. It is a powerful tool for shaping appropriate behaviors. Extinction, selective attention, praise, and differential reinforcement of other behaviors (DRO) are examples of contingent



reinforcement. For example, the patient is praised for all appropriate behaviors, especially those facilitating daily transitions such as the timely completion of ADLs, grooming, exercise effort, social skills, following unit rules and directives, and working toward psychological treatment goals. A token economy works well as a structured system for delivering contingent response to behavior. For oppositional behavior among individuals with PWS, a response cost intervention is recommended. It will be necessary to post the rules and expectations; delineate rewards (tokens) for achieving expectations, and define the cost (loss of rewards) for not achieving the desired results.

### 3. Psychological therapies

Throughout inpatient hospitalization, individual and group therapy sessions focus on acceptance of and building expectations for a continuation of the therapeutic milieu following discharge. An appreciation for intellectual level and learning style is essential; adapting the daily plan to meet the individual's unique pattern of strengths and weaknesses can lead to better compliance during the hospital stay. For example, an individual with receptive and expressive language disability will not perform well in a group context. Psychological testing should be available by history to ascertain overall intellectual ability. Neuropsychological testing can be requested to elucidate learning disorders, and strategies for adaptation can be tested during the hospital stay and taught to the family or other caretakers before discharge.

The utility and effectiveness of psychological interventions is based entirely upon an individual's verbal and intellectual abilities. High-functioning individuals with PWS may benefit from all psychotherapeutic and behavioral modalities. Clinical experience suggests that young adults with PWS have the capacity to realize that their syndrome may limit their potential for independence and that many of the life goals that they share with typical peers and siblings may never be actualized. They need support as they grieve the loss of a "normal" life. Social and family situations that are usually joyful, such as college graduations, marriages, and births, may be reminders of unachievable milestones and precipitate dysphoric responses. These situational crises can be addressed through traditional psychotherapy using interpersonal and cognitive strategies with the individual and the family.

Lower-functioning individuals with limited insight may require individual therapy with supportive and psychoeducational goals such as minimizing stress, enhancing coping abilities, and improving participation and compliance with the inpatient program. Strategies and modalities for relaxation (progressive muscle relaxation, deep breathing, and occasionally visual imaging), anger management, social problem solving, and social skills training may be prescribed, taught to the individual with repetition and drill, woven into the fabric of the daily plan, and implemented with prompts, cues, and supervision.

### 4. Psychotropic medication

The use of psychotropic medication is determined by (1) the patient's response to behavioral and eco-environmental interventions, (2) psy-

chiatric diagnosis, (3) the nature of targeted symptoms, and (4) severity of impairment. There is no syndrome-specific medication. Effort is directed toward eliminating unnecessary medications that may be producing unwanted side effects as well as selecting the best medication for improving adaptive function.

Several observations about the use of psychotropic medication in the referral population of individuals with PWS are offered. First, dose titrations should be made in small increments because individuals with PWS may respond to lower doses of psychotropic medication. Second, clinical experience with the referral population suggests that activation as well as discontinuation syndromes occur with selective serotonin reuptake inhibitors (SSRIs), nonselective serotonin reuptake inhibitors (NSRIs), and even some psychostimulants at a rate that exceeds the neurotypical population. Third, it is assumed that the sedating side effects of some agents could increase respiratory compromise due to hypoventilation in obese individuals. Finally, the risk of hyponatremia associated with the use of certain classes of medication (anticonvulsants, SSRIs, and atypical neuroleptics) should be kept in mind, especially during upward titration of the dose.

Pharmacokinetic variations that should be considered among individuals with PWS are summarized below:

- High fat/lean ratio in body composition (even in normal weight individuals with PWS) may affect metabolism and bioavailability of fat-soluble medications.
- Low muscle mass may alter the presentation of extrapyramidal side effects of typical and atypical neuroleptics.
- Doses of medication and schedule of administration should take into consideration persistent prepubertal status due to hypothalamic hypogonadism.
- Concurrent administration of calcium for osteoporosis may affect absorption and action of the psychotropic medication.

##### 5. Family/group home staff involvement

Preparation for discharge begins before admission. Family education is an intense process that continues throughout hospitalization. Training sessions are attended by parents, step-parents, and siblings, as well as involved extended family members (aunts, uncles, and grandparents). School personnel, in-home support personnel, local mental retardation and developmental disabilities (MRDD) staff, as well as supervisors, school nurses, nutritionists, group home staff, and mental retardation program administrators also are invited.

The goal of this training is to teach the caretakers how to devise, within the limits of their own situation, a therapeutic milieu similar to the one shown to be effective during hospitalization. The plan mimics the hospital program by providing the same special structure, expectations, consequences, and schedule. The hospital exercise program to which the patient has become accustomed is duplicated or modified as needed for the home environment.

Psychoeducational intervention is the keystone of relapse prevention. Eco-environmental interventions (i.e., the treatment plan) can be developed only after a thorough review of predisposing, precipitating, and perpetuating factors. This information provides a basis for understanding the strengths and weaknesses in the system of care. The results of the patient evaluation and the comprehensive formulation are provided to the family/staff to assist their understanding of the acute and chronic aspects of the crisis that precipitated hospitalization. In this way they are prepared to make the changes that will be required to meet the individual's needs. Finally, the family/staff work with the team to develop an action plan for how to change the environment, the daily structure, and the existing behavioral patterns in order to meet the individual's needs. The degree of additional support necessary to implement the treatment plan is assessed and a therapeutic network of professional and extended family supports may be identified for recruitment as needed.

## 6. Disposition planning

Disposition planning includes an examination of all available short-term and long-term resources and living arrangements. Outpatient treatment, school- and/or workshop-based interventions, and wrap-around or habilitative services help families to provide for the needs of their child in the home. Residential treatment or group home placement is explored when appropriate, especially in the case of patients with an exceptionally high need for structure and supervision. Persons with PWS are rarely well managed in facilities that do not have prior experience with the syndrome or a commitment to develop a program specifically suited for individuals with the syndrome. The Prader-Willi Syndrome Association (USA) is a valuable resource for families, and membership is encouraged.

Psychiatric follow-up for individuals with PWS can be challenging. "Finding Psychiatric Help for Your Child" is a monograph pertaining to this topic available at the PWSA (USA) Web site ([www.pwsausa.org](http://www.pwsausa.org)).

## Conclusion

Prader-Willi syndrome is a genetic disorder with neurologic abnormalities affecting cognition, behavior, and energy balance. The complications of the disorder, when environmental controls are not in place, are chronic disability and cardiopulmonary deterioration from morbid obesity in addition to the complications of uncontrolled diabetes. Inpatient crisis intervention is briefest when done early on during the process of deteriorating food control and weight gain and prevents a pattern of multiple acute-care hospitalizations.

Behavior problems complicate the management of persons with PWS and sometimes necessitate inpatient hospitalization. Psychiatric vulnerability appears to be a direct result of the stress sensitivity associated with this condition. A specialized team with experience working

with Prader-Willi syndrome can provide successful intervention for patients in medical or behavioral crises who are not responding to outpatient interventions. The therapeutic milieu is the definitive intervention for both food and behavioral management. Although it is typically implemented during an inpatient hospitalization, it can be translated through training to other settings including the home, school, and community living situations.

The use of psychotropic medication is based on psychiatric diagnosis and the nature and severity of psychiatric symptoms. The diagnosis of Prader-Willi syndrome does not determine the selection of psychotropic medication but rather informs the interpretation of symptoms and the resulting diagnostic formulation, which in turn guide the psychiatrist in the choice of medication.

## Glossary

*ACE inhibitors*—(angiotensin converting enzyme inhibitors) medication used in treating left heart failure.

*adipose*—fat tissue.

*asymptomatic*—without symptoms.

*azotemia*—a build-up of nitrogen waste products in the blood when kidney function is deficient.

*BiPAP and CPAP*—Bi-level Positive Airway Pressure and Continuous Positive Airway Pressure.

*cardiomegaly*—enlarged heart.

*cellulitis*—infection of tissue, often a complication of venous stasis and lymphedema (serum).

*creatinine*—a measure of kidney function.

*CO<sub>2</sub> narcosis*—toxicity of the brain from excessive amounts of retained CO<sub>2</sub>, resulting in decreased breathing.

*dissociative state*—a mental condition causing an incomplete awareness of pain or other stimuli.

*echocardiography*—sonar exam of the heart; gives dynamic information about heart function.

*edema*—excess fluid in tissue.

*deconditioning*—weakness and loss of flexibility from inactivity.

*glycemic*—pertaining to blood sugar.

*heart failure*—the pump function of the heart is not adequate to meet the body's needs.

*hematocrit*—measures the proportion of red blood cells to serum in the blood.

*hemoglobin*—measures the oxygen carrying capacity of the blood.

*hepatic*—having to do with the liver.

*hypercapnia*—high CO<sub>2</sub>; very high levels of CO<sub>2</sub> cause coma and cessation of breathing.

*hyperkalemia*—high potassium in the blood.

*hyperglycemia*—high blood sugar.

*hypoglycemia*—low blood sugar.

*hyponatremia*—low sodium in the blood.

*hypoperfusion*—undersupply of blood to tissue due to low pressure.

*hypothermia*—low body temperature.

*hypoxemia, hypoxia*—low oxygen in the blood.

*iatrogenic*—caused by medical intervention.

*interstitial*—the space in tissue between the cells.

*intubation*—breathing tube placed in windpipe, enables the use of a ventilator.

*ischemia*—inadequate oxygen to tissue, usually due to inadequate blood flow.

*lymphatic*—the vessels in the body that carry tissue fluid back to the heart.

*lymphedema*—fluid build-up in one part of the body as a result of damage to the lymphatic vessels.

*monilial*—yeast, produces red rashes and skin breakdown in areas of skin that are allowed to remain moist.

*pitting*—finger pressure on edema will often produce a depression that remains visible for several seconds or longer; physicians often use this sign to help detect edema.

*pulmonary edema*—excess fluid in the lungs.

*pulmonary hypertension*—increased blood pressure in the lungs.

*pulmonary vascular resistance*—roughly positively related to the blood pressure in the lungs.

*radiograph*—X-ray picture.

*REM*—rapid eye movement, one of the deeper stages of sleep associated with dreaming.

*renal*—having to do with the kidneys.

*respiratory failure*—breathing is inadequate to rid the body of CO<sub>2</sub>, which builds up in the blood.

*superficial venous*—pertaining to the veins near the surface.

*thrombosis*—blood clot formation.

*thromboembolic*—pertaining to blood clots that travel to another part of the body.

*tracheotomy*—surgical opening in neck to bypass the upper airway.

*transaminase*—a measure of liver function.

*venous stasis*—poor return of blood through the veins in the legs.

*ventilation*—breathing.

*ventricular failure*—the right or left ventricle of the heart is unable to meet the body's demands.

*ventriculomegaly*—enlarged ventricle.

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# Appendix B

## A Comprehensive Team Approach to the Management of Prader-Willi Syndrome

*Note:* This document represents the consensus of an international meeting of PWS specialists on April 24, 2001, sponsored by the International Prader-Willi Syndrome Organization (IPSWO) and funded through a grant from Pharmacia Corporation. The consensus statement was originally edited by Dr. Urs Eiholzer in 2001 and subsequently revised with the assistance of Dr. Phillip D.K. Lee in 2004.\*

### Meeting Participants

*Moderator and Presenter:* Urs Eiholzer, MD, Head, Foundation Growth Puberty Adolescence Zurich, Switzerland

*Other Presenters:*

Margaret Gellatly, BSc (Hons), SRD, Hon Dietary Adviser, Prader-Willi Syndrome Association (UK), Chelmsford, UK

Phillip D.K. Lee, MD, Director, Division of Endocrinology and Metabolism, Children's Hospital of Orange County, Orange, California, USA [*Note:* Dr. Lee is currently Chief Scientific Officer, Immuno-diagnostic Systems Ltd., Bolden, Tyne & Wear, UK]

Martin Ritzén, MD, Professor, Department of Pediatric Endocrinology, Karolinska Hospital, Stockholm, Sweden

Barbara Y. Whitman, PhD, Professor, Department of Developmental Pediatrics, St. Louis University, Cardinal Glennon Children's Hospital, St. Louis, Missouri, USA

\*In 2003, a warning label was added to Genotropin/Genotonorm (Pfizer), the growth hormone preparation labeled for treatment of PWS. The warning label includes recommendations for evaluation of sleep and breathing disorders and screening for morbid obesity prior to initiation of therapy. The Clinical Advisory Board of the Prader-Willi Syndrome Association (USA) subsequently issued its own guidelines regarding sleep, breathing, and respiratory evaluation. These subjects are discussed extensively in Chapters 5 and 7 of this volume and are not specifically addressed in the Comprehensive Care guidelines.

*Panelists:*

Giuseppe Chiumello, MD, Professor, Università degli Studi di Milano, Clinica Pediatrica III Ospedale San Raffaele, Milan, Italy

Yukihiro Hasegawa, MD, Chief, Endocrinology, Metabolism and Genetics Unit, Tokyo Metropolitan Kiyose Children's Hospital, Tokyo, Japan

Priv-Doz Dr med Berthold P. Hauffa, Abt. F. pädiatrische Hämatologie/Onkologie und Endocrinologie, Universität GHS Essen, Essen, Germany

Maïthé Tauber, MD, Professor, Children's Hospital Toulouse, Toulouse, France

## Introduction

The treatment of children with Prader-Willi syndrome (PWS) represents a challenge, particularly in the field of pediatric endocrinology. The handicaps and problems of affected children are manifold, more so than in any other typical disease of pediatric endocrinology, perhaps with the exception of craniopharyngioma. Therefore, management of children with PWS may be most successful with a team approach to comprehensive care. We thank Pharmacia Corporation for organizing a workshop on such an approach in St. Julians, Malta, on April 24, 2001.

The reader will notice that the development of a comprehensive professional team approach to PWS has only just begun. Much work remains to be done, primarily to define what, exactly, a "comprehensive team approach" to PWS means. For example, it appears necessary for one highly experienced specialist team member to assume leadership, to allow patients and their families to interact with one single professional. Furthermore, growth hormone (GH) treatment has become a very important tool in the management of PWS. Nevertheless, it must be emphasized that without a comprehensive team approach, especially to control weight gain, optimize dietary intake, and provide family psychosocial support, children with PWS may continue to suffer from excessive weight gain and major behavioral problems despite the beneficial effects of GH.

Some centers have a great deal of experience and know-how in managing PWS. This know-how, however, is most often attributable to the experience of a single person. Through intensive study of the experience and strategies of such centers and individuals, a professional comprehensive team approach can be developed that will allow centers all over the world to offer optimum care to their patients with PWS.

Prader-Willi syndrome (PWS) is characterized by infantile hypotonia; short stature; small hands and feet; increased body fat; decreased muscle mass; scoliosis; reduced resting energy expenditure (REE); reduced bone mineral density (BMD), which may lead to osteopenia and osteoporosis; hypogonadism; hypothalamic dysfunction; and a particular facial appearance. These clinical features are accompanied by hyperphagia, cognitive disabilities, and behavioral problems, including skin picking. In approximately 70% of affected individuals, the

syndrome is the phenotypic expression of a complex genetic disorder resulting from a de novo deletion of the “PWS region” located on the proximal long arm of the paternal copy of chromosome 15 (at bands 15q11.2–15q13). Maternal disomy 15 (inheritance of both chromosome 15 copies from the mother, with no paternal copy) is seen in about 25% of individuals with PWS. Chromosomal translocations involving the paternal “PWS region” of 15q and imprinting center defects account for a small percentage of cases.<sup>1</sup> Prader-Willi syndrome and Angelman syndrome (an entirely different clinical syndrome involving defects in the maternal copy of 15q) were among the first examples in humans of genomic imprinting, or the differential expression of genetic information depending on the parent of origin. Prader-Willi syndrome is one of the more common conditions seen in genetics clinics worldwide, occurring in an estimated 1:10,000–25,000 individuals, and is the most common syndrome associated with morbid or life-threatening obesity. For affected individuals, the various clinical manifestations of PWS are major causes of morbidity and social limitation. Learning ability, speech and language, self-esteem, emotional stability, social perception, interpersonal functioning, and family dynamics, in addition to cognition and behavior, are all adversely affected in PWS.

A panel of international experts on PWS was convened to share their clinical experience and to identify strategies for managing PWS. The panel agreed that, because PWS produces various adverse functional as well as metabolic effects, individuals with PWS require a variety of interventions to optimize their growth and development. These include growth hormone (GH) replacement; dietary management; physical and occupational therapy; speech, language, and learning disability services; behavior management; and family interaction, support, and care. Children with PWS should be evaluated and treated in a multidisciplinary clinic that is managed by a nurse coordinator and staffed by a physician specialist in PWS, geneticist, psychologist, and dietitian. Ancillary resources should include support by neurology, physical therapy, social services, and educational services, as well as readily available facilities for measuring body composition (including whole-body DEXA) and exercise physiology. The Table (B.1) lists the components of the initial evaluation and testing. Follow-up visits are recommended at 6-month intervals for patients receiving GH therapy. In the majority of patients puberty will not occur, and gonadal steroid replacement therapy should be considered for them on the basis of clinical and DEXA findings.

## **GH Effects on Physical Parameters in PWS**

Dysregulated GH secretion associated with deficient GH responses is a principal cause of short stature in the majority of individuals with PWS. It is probably also an important contributor to the decreased muscle mass and osteopenia in patients with PWS, whereas hypogonadotropic hypogonadism is the probable primary cause of osteopenia and osteoporosis in these patients.<sup>2</sup> Evidence is mounting that GH

Table B.1. Recommended Components of the Initial Visit to a Multidisciplinary Prader-Willi Syndrome Clinic

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <div> Evaluation <ul style="list-style-type: none"> <li>• Confirmation of diagnosis, genetic counseling</li> <li>• Complete examination</li> <li>• Dietary evaluation and counseling</li> <li>• Physical therapy evaluation (developmental, neuromuscular)</li> <li>• Psychological evaluation and recommendations</li> <li>• Educational evaluation and recommendations</li> <li>• Initial discussion of growth hormone therapy and approval process</li> </ul> </div> <div> Testing <ul style="list-style-type: none"> <li>• DNA studies</li> <li>• IGFBP-3, IGF-I, thyroid panel, lipid panel (other lab tests as clinically indicated)</li> <li>• Screening for glucose intolerance if patient is obese (fasting glucose, glycated hemoglobin, oral glucose tolerance test, if indicated)</li> <li>• Body composition analysis (DEXA, anthropometry, or other method)</li> <li>• Psychological and/or educational testing</li> <li>• Strength and endurance testing</li> </ul> </div> |
| <div> DEXA = dual-energy X-ray absorptiometry; IGF-I = insulin-like growth factor-I; IGFBP-3 = IGF binding protein-3. </div>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |

deficiency may contribute not only to the abnormal growth pattern but also to the excess of body fat and the lean body mass deficit.<sup>3,4</sup> Growth hormone treatment of children with PWS normalizes linear growth,<sup>5–10</sup> promotes growth of lean body mass,<sup>6–8,11,12</sup> and decreases fat mass.<sup>6–8,11,12</sup> However, the benefits associated with GH therapy can be optimized and maintained only in conjunction with a multidisciplinary approach that emphasizes comprehensive care for the complex neurobehavioral and endocrine needs appropriate for the patient’s age.

The role of GH as a component of the overall management of PWS has been studied extensively in the United States, Switzerland, and Sweden.

American Experience

Parra and co-workers observed in 1973 that a deficient GH response to pharmacologic stimuli appeared to be related to the abnormal growth pattern in patients with PWS.<sup>13</sup> In 1987, Lee and colleagues reported for the first time that GH therapy led to significant increases in the linear growth rate of patients with PWS.<sup>6</sup> Patients in their study initially had low serum levels of GH and insulin-like growth factor-I (IGF-I); during GH therapy, levels of IGF-I normalized. These results indicated that the low GH levels observed in these cases were not an artifact of obesity and supported the premise that the poor linear growth in patients with PWS might be caused by a true deficiency of GH. In 1993, Lee and collaborators reported the results of an uncontrolled trial of GH therapy in 12 obese children with PWS and associated chromosome 15 abnormalities.<sup>14</sup> All 12 children initially had low serum levels of GH, IGF-I, IGF-2, IGF binding protein-3 (IGFBP-3), and osteocalcin. These levels normalized and height velocity increased during GH therapy. Dual-energy X-ray absorptiometry (DEXA) at baseline revealed in-

creased fat mass, normal (not weight-corrected) BMD, and very low lean body mass. Within 3 months of the patients' beginning GH therapy, DEXA revealed variable changes in fat mass and increased BMD and lean body mass, with redistribution of fat mass from the trunk to the thighs. The majority of parents reported improved behavior and appetite control. The decreased GH secretion commonly seen in children with PWS had been considered by some to be an effect of obesity, but reduced GH secretion had also been found in non-obese children with PWS.

Angulo and colleagues studied 33 obese and 11 non-obese children with PWS to determine whether the suboptimal GH secretion was an artifact of obesity.<sup>15</sup> Spontaneous GH secretion was measured over 24 hours, and GH secretion was provoked by insulin, clonidine, and levodopa. Of the 44 subjects, 40—including 10 non-obese children—failed to respond to at least two of the stimuli, and 43 had reduced spontaneous 24-hour GH secretion. The investigators concluded that the GH deficiency seen in PWS is not a consequence of obesity but rather a significant contributor to the decreased growth velocity and increased adiposity typical of the syndrome.

In a controlled trial reported in 1999, Carrel and associates assessed the effects of GH therapy on growth, body composition, strength and agility, respiratory muscle function, REE, and fat utilization in 54 children with PWS, all of whom had low peak stimulated GH levels at baseline.<sup>6</sup> Thirty-five children received GH at a dose of 1 mg/m<sup>2</sup>/day and 19 were untreated. After 12 months, the GH-treated children showed significantly increased height velocity, decreased percentage of body fat, and improved physical strength, agility, and respiratory muscle function, although there was no significant increase in REE. The investigators concluded that GH therapy, in addition to its effect on growth and body composition, may have value in improving some physical disabilities experienced by children with PWS. After 24 months of GH therapy, patients had experienced sustained decreases in fat mass, increases in lean body mass,<sup>7</sup> and improvements in physical strength and agility.<sup>8</sup> Height velocity remained significantly higher than at baseline ( $P < 0.01$ ), although the growth rate slowed between 12 and 24 months. To achieve these encouraging results, the investigators suggested, GH therapy should be started early; GH therapy started in middle to late childhood may not be capable of normalizing the percentage of body fat in patients with PWS.<sup>7</sup>

At baseline, 70% of subjects had mild to moderate scoliosis on spine films.<sup>8</sup> During the first year of the study, no significant difference in scoliosis progression was seen between the GH-treated group (from a mean of 9.2° at baseline to 12.1°) and the control group (from 14.7° to 16.6°). During the second year, the mean change in curve measurement in the GH-treated group also was not significant.

### Swiss Experience

Disturbed satiation and energy expenditure are basic defects in PWS. Reduced muscle mass appears to be the consequence of decreased



physical activity, which is probably caused by the central nervous system defects. Reduced muscle mass, in turn, is the cause of the decreased energy requirement. The benefit of GH therapy for children with PWS, according to Eiholzer's group, is an increase in lean body mass and a subsequent increase in REE. If energy intake is not increased, these alterations lead to a reduction of energy stores, mainly of body fat, and a dramatic change in phenotype. However, even though height and weight are normalized during GH treatment, children with PWS must maintain their energy intake at about 75% of the intake of healthy children to stabilize their weight for height. Such a reduction of food intake is possible only through close, strict parental supervision, and this is a major reason why families caring for a child with PWS need psychosocial support. Following is a short summary of the Swiss experience with GH therapy.

Eiholzer and l'Allemand described 23 children with genetically confirmed PWS and divided them into three groups: group 1 comprised young children who were not yet obese; group 2, prepubertal overweight children; and group 3, pubertal overweight children. All were treated with GH 24U/m<sup>2</sup>/week (~0.037 mg/kg/day) for a median of 4 years (range, 1.5 to 5.5 years).<sup>9</sup> In group 1, weight and weight for height were lower than normal before treatment and continuously increased up to the normal range during treatment. In group 2, a dramatic height increase and drop in weight for height showed clearly that these obese children had become not only taller but also slimmer with treatment. In group 3, however, the effect of GH on growth and weight was rather limited. The investigators concluded that if treatment is instituted early enough, growth becomes normal and height predictions reach the parental target height. This effect of exogenous GH on growth has so far been described only in children with GH deficiency.

Most importantly, although loss of fat mass, as determined by DEXA,<sup>12</sup> in the older children (group 3) was considerable with exogenous GH administration, fat mass was still in the upper-normal range. The influence of exogenous GH on muscle mass in PWS was found to be limited. Catch-up growth in muscle mass, as estimated by lean mass, was observed only during the first 6 months of therapy; thereafter, muscle mass increased in parallel with height. Therefore, it was deduced that muscle mass remained relatively decreased.

Improvement in body composition is the main goal in the treatment of children with PWS. According to the Swiss experience, the changes in body composition during GH therapy result from several therapeutic interventions. It is critical to maintain control of nutrient intake during GH treatment, in accordance with the reduced energy requirements in PWS. In children with PWS, energy requirements are about 50% below those of healthy children.<sup>17</sup> Growth hormone treatment does not change the feeling of satiety but increases the energy expenditure resulting from the increase of lean mass by an estimated 25%, as shown by another Swiss study.<sup>18</sup> Weight for height and BMI decrease during GH treatment only if energy intake is not increased at the same time. It is therefore imperative that parents continue to keep patients' food

consumption under control with the same rigidity as before the start of GH treatment.

Hypothesizing that increased muscle mass in infants may positively influence motor development, Eiholzer and colleagues used the Griffith test<sup>19</sup> to study psychomotor development in 10 young, underweight children with PWS during the first year of GH treatment.<sup>20</sup> At baseline, the children were significantly more retarded on the “locomotor” and “hearing and speech” scales than on the other scales. During GH therapy, locomotor capabilities increased significantly, whereas hearing and speech remained unchanged. The treated children started walking unassisted at an average age of 24.1 months, about 4 to 6 months earlier than untreated children with PWS. Motor development thus seems to be improved by GH therapy.

In older children, improvement in physical performance is—in the opinion of the parents—the most important therapeutic effect of GH.<sup>21</sup> After 1 year of GH therapy, physical performance, as assessed by ergometry, significantly increased in peak and mean power in four prepubertal 7-year-old obese children. Such improvement in physical performance leads to an increase in activity, which, together with the disappearance of the obese phenotype, may relieve patients and their families of a major stigma that accompanies PWS, improving their quality of life.

The Swiss group was also able to show for the first time that insulin secretion in children with PWS is delayed and lower than that shown in otherwise normal, nonsyndromal obese children and in children without PWS on GH therapy.<sup>22</sup> In addition, the increase in fasting insulin and insulin resistance seen in children with PWS during GH therapy is transient.<sup>22</sup> Three years of GH therapy did not impair carbohydrate metabolism, but rather counteracted the potential GH-induced insulin resistance by decreasing fat mass and increasing lean mass. Since normal insulin sensitivity remains preserved, the investigators speculated that the primary mechanism for the development of diabetes in PWS is a reduced secretory capacity of pancreatic beta cells that persists despite GH administration.

According to the Swiss researchers, certain aspects of lipid metabolism differ in PWS and non-PWS obesity. In PWS, triglyceride levels are normal (although still correlated with abdominal obesity), but LDL cholesterol levels are elevated and HDL cholesterol levels are decreased.<sup>23</sup> These lipid levels normalize during GH therapy, but the changes are not associated with changes in body fat and probably are caused by the direct effects of GH deficiency and exogenous GH administration on cholesterol metabolism, as described in adult patients with GH deficiency.<sup>24</sup>

### Swedish Experience

Despite the evidence from uncontrolled trials that GH therapy is beneficial in PWS, a number of pediatric endocrinologists continued to believe that the GH deficiency seen in the syndrome was a result of the characteristic obesity, and they were concerned that treatment with

exogenous GH would negatively affect endogenous GH secretion. For this reason, a controlled study was conducted to assess the effects of GH therapy on growth, body composition, and behavior in prepubertal children with PWS.

Lindgren and co-workers reported preliminary results<sup>25</sup> of this study in 1997 and 5-year results<sup>10</sup> in 1999. After a 6-month evaluation period, patients with PWS between the ages of 3 and 7 years were randomized into group A ( $n = 15$ ), which received GH 0.1 IU/kg/day (0.033 mg/kg/day) for 2 years, or group B ( $n = 12$ ), which received no treatment for the first year and GH 0.2 IU/kg/day (0.066 mg/kg/day) during the second year. After 2 years, all children stopped GH therapy for 6 months and then restarted GH therapy at a dose of 0.1 IU/kg/day (0.033 mg/kg/day). The 6-month GH-free interval was included to prove that the effects of GH therapy were reversible and to compare the effects of the low and high doses.

Before GH therapy, all patients had low 24-hour levels of GH and IGF-I and low levels of insulin. During the first year of the study, IGF-I levels increased rapidly to supranormal values in group A (GH therapy) but remained essentially unchanged in group B (no treatment). With respect to growth, height velocity standard deviation scores (SDS) increased from  $-1.9$  to  $6.0$  during the first year of GH therapy in group A, followed by a lower rate of increase during the second year. In group B, height velocity SDS decreased slightly during the first year of the study (no treatment) but increased rapidly from  $-1.4$  to  $10.1$  in the second year of the study (GH therapy). When GH therapy was stopped for 6 months, height velocity declined dramatically in both groups; height SDS followed a similar pattern. Growth hormone therapy reduced the percentage of body fat and increased the muscle area of the thigh; isometric muscle strength also increased. In addition, parents reported that GH therapy seemed to have psychological and behavioral benefits, which were reversed after treatment was stopped.

Five-year follow-up data on 18 of the children were published in 1999.<sup>10</sup> Following resumption of GH therapy after the 6-month discontinuation, height SDS again increased. Body mass index SDS stabilized at  $1.7$  for group A ( $n = 9$ ) and  $2.5$  for group B ( $n = 9$ ). In 16 children, levels of fasting insulin, glucose, and the  $A_{1c}$  fraction of glycated hemoglobin remained within normal ranges. The remaining two children developed non-insulin-dependent diabetes mellitus following a rapid weight gain, but glucose homeostasis returned to normal when GH was discontinued. Unpublished 7-year follow-up data show that height has been normalizing with prolonged treatment.

## Clinical Management of PWS-Associated Behaviors

By adolescence, behavioral problems characteristically have evolved as a major issue for patients with PWS and their families. Adolescents with PWS have been described as stubborn, impulsive, manipulative, irritable, mood-labile, angry, perseverative, egocentric, demanding,

and prone to rage episodes when frustrated. Transitioning from one activity to another becomes increasingly difficult, and there is a tendency to confuse day with night. Thus, the food-related behavior constellation, although dramatic, is just one of many neurobehavioral abnormalities characterizing this disorder, and the food behavior often is the easiest to manage.

These behavioral traits are frequently accompanied by depression, obsessions, or even frank psychoses, and they ultimately are responsible for the inability of adults with PWS to succeed in alternative living and work placements. Interestingly, many of the characteristic behaviors of patients with PWS, including cognitive rigidity, hoarding behavior, impaired judgment, denial of deficits, inability to self-monitor behavior, and interpersonal conflicts, are also seen in patients with traumatic brain damage. In patients with PWS, however, the brain damage is genetic and, unlike traumatic brain damage, appears to affect the entire brain. Prader-Willi syndrome may thus be characterized as a pervasive developmental neurobehavioral syndrome whose behavioral manifestations reflect a distributed central nervous system dysfunction that has yet to be fully described either anatomically or biochemically.

In addition to behavioral problems, four cognitive difficulties have been identified in patients with PWS: global mental retardation, language processing problems, learning disability associated with short-term memory and sequencing deficits<sup>27</sup> and failure to develop the ability to apply knowledge in new situations (metacognitive ability). Most patients with PWS score between 60 and 80 on IQ tests, and at least some have IQ scores in the 90s or somewhat higher. Functional aptitude, however, is entirely independent of test scores and appears to be related more to the degree of cognitive rigidity. Impaired metacognitive ability prevents patients with PWS from utilizing their typically extensive compendium of facts in a practical or productive manner. Difficulty with sequencing and language deficits underlies most of the behavioral problems and the inability to change some behaviors. Sequencing difficulty extends beyond simple numerical applications and includes an inability to recognize cause-and-effect sequences. This particular problem necessitates an entirely different approach to traditional behavior management, since patients with PWS fail to link punishment or reward with an antecedent behavior.

Many patients with PWS who frequently exhibit problem behaviors are able to alter these behaviors when environmental changes are instituted. These changes require creativity, hard work, and, often, many months before a behavior is altered, and some environmental and family situations are unalterable. It is particularly difficult when parents disagree about the management approach. Children with PWS who have the worst behavior in terms of depression and anxiety come from families in which parents report the highest level of conflict over child rearing. Although this is also true for normal children, children with PWS do not have the flexibility seen in normal children. Therefore, family therapy is recommended as soon as the diagnosis of PWS is made in an infant or young child.

For many patients with PWS, problem behaviors are resistant to most attempts at behavioral management, and pharmacologic interventions are often considered when this becomes clear. Unfortunately, psychopharmacologic agents frequently worsen problem behaviors in these individuals. A survey of parents of children with PWS conducted between 1989 and 1993 revealed that almost every available psychotropic agent had been prescribed to manage behavioral problems.<sup>28,29</sup> Most agents either were ineffective or increased the occurrence of targeted symptoms; only three—haloperidol, thioridazine, and fluoxetine—were effective.<sup>30</sup> More recently, it has been found that all serotonin specific reuptake inhibitors seem to have a nonspecific behavior-stabilizing effect, characterized by fewer outbursts, a marked reduction in irritability, and less perseveration, but with no specific antidepressant effect.<sup>31</sup> Other psychotropic drugs, such as the antipsychotic agent olanzapine and the anticonvulsant agent divalproex sodium, may have an effect.<sup>31</sup> It must be emphasized, however, that any single agent may produce a dramatically beneficial response in some patients with PWS and a dramatically adverse response in others, and many patients with PWS have idiosyncratic reactions to psychotropic drugs. Those with PWS require only one fourth to one half the standard dose of a psychotropic drug to achieve a benefit; increasing the dose to “normal” often results in toxicity and a return of the problem behavior.<sup>31</sup> In general, psychotropic medication should be used only when all other interventions, including behavioral modification and environmental changes, have failed.

It should also be noted that appetite-suppressing medications have been ineffective in controlling food-seeking behavior and overeating.<sup>1</sup> Pharmacologic agents, including the amphetamines and agents that block nutrient absorption, which are often effective for weight control in non-PWS obese population, do not appear to alter the brain signals, or perhaps peripheral signals, that drive patients with PWS to seek food and overeat. Until a medication is discovered that can accomplish this goal, good management depends entirely on environmental control, protection against overeating, and an understanding caregiver who recognizes that the constant feeling of hunger experienced by these patients underlies some of their irritability and other behavior characteristics.

With regard to the effect of GH therapy on PWS behavior in the setting of behavioral difficulties and refractoriness to psychopharmacologic agents, surveys of parents indicate that some behaviors improve and none deteriorate.<sup>26,32</sup> Since the behavior of children with PWS tends to deteriorate over time, the absence of deterioration is, in fact, a positive outcome. Specific behavioral benefits of GH therapy, as reported anecdotally by parents, included increased energy, increased activity without the need for encouragement, improved personal hygiene, less “annoying” behavior, increased assumption of responsibility, and less perseveration.<sup>26,32</sup> In addition, attention span and compliance seemed to improve and anxiety, depression, and obsessive thoughts decreased, although there was no impact on obsessive-compulsive behavior or improvement in school performance. Growth hormone therapy also

produced positive effects on physical appearance, usually within 3 to 6 months of patients' starting treatment. Appearance of the hands, feet, and trunk normalized in all GH recipients, and appearance of the head normalized in 81%. Such changes may positively affect patients' social interaction. Furthermore, 97% of patients had more energy and 83% spontaneously increased their level of physical activity without parental prodding.

## **Improving Quality of Life in Patients with PWS: Diet, Exercise, and Lifestyle Changes**

Surveys performed in the United Kingdom in 1989 and 1999 have provided useful information about the impact of lifestyle changes on PWS. From the standpoint of diet, two distinct phases of PWS are apparent: initial failure to thrive and subsequent obesity.

Failure to thrive results primarily from hypotonia, which makes sucking difficult during infancy. Nasogastric tube feeding may be necessary for as long as 2 months to meet energy requirements. Signs of poor feeding in infants with PWS include changes in the voice or cry, coughing while swallowing, excessive drooling, frequent vomiting, constipation, respiratory infections, irritability during feeding, slow intake, and poor weight gain. For infants who are able to suck, specially designed nipples can reduce the energy expenditure. Early weaning to soft food will reduce energy requirements; introduction of solids is accompanied by a lessening of appetite for milk.<sup>33</sup> However, some 33% of older infants with PWS are unable to eat soft food normally acceptable at 1 year, and children with PWS typically lag far behind children without PWS in their transition to solid food, with 42% of children with PWS unable to chew some solid foods at the age of 5 years.<sup>34</sup>

The change from failure to thrive to excessive weight gain generally occurs between 2 and 4 years; there seems to be a recent shift toward the younger age. Despite their reduced energy requirement, these children are obsessed with food and engage in food seeking and food stealing. Overeating may be due to the prolonged eating drive that results from their disturbed feelings of satiety.<sup>35</sup> The vast majority of parents of children with PWS have attempted to control their children's weight, but dietary compliance is poor. Severe caloric restriction for short periods at home or for longer periods in the hospital setting may be helpful, but most families feel that no intervention will help.

Increased physical activity can increase energy expenditure, promote negative energy balance, raise the post-exercise metabolic rate, build muscle mass, prevent osteoporosis, improve scoliosis, and enhance the overall sense of well-being. However, very few patients with PWS seem to participate in a structured exercise program. Aerobic exercise, toning and strengthening, flexing and stretching, and formal physiotherapy are all useful for patients with PWS. Activities they may find acceptable include bicycling, skating, jumping on a trampoline, dancing, and ball playing.



Lifestyle changes that can be implemented certainly include control of food-seeking and food-stealing behaviors but also must encompass social integration and independence. Specific environmental controls designed to limit hyperphagia include locking places where food is stored, restricting access to money or credit cards, and prohibiting participation in food preparation. Unfortunately, many of these impositions and limitations may actually discourage social integration and independence.

## Summary and Conclusion

Because of its many physical and behavioral manifestations, PWS should be managed in a multidisciplinary setting that emphasizes comprehensive care. Clinical trials confirm that GH treatment of children with PWS normalizes linear growth, promotes an increase in lean body mass, and decreases fat mass. However, due to the complex nature of the syndrome, the long-term benefits of GH can be optimized and maintained only in conjunction with dietary control and counseling, physical therapy, and psychological and educational evaluation and support.

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