Appendices

Appendix A

First Published Report of Prader-Willi Syndrome

Note: The first published description of the condition that we now know as Prader-Willi syndrome was authored by Swiss doctors Andrea Prader (Figure A.1), Alexis Labhart (Figure A.2), and Heinrich Willi (Figure A.3) and appeared in the journal *Schweizerische medizinische Wochenschrift* (*Swiss Medical Weekly* [*SMW*]) in 1956. Thanks to Dr. Urs Eiholzer, a protégé of Dr. Prader, and with copyright permission from the publisher of *SMW,* we are able to reproduce that first report in the original German as well as in an English translation with footnotes, commentary, and historical photographs. Dr. Phillip D.K. Lee assisted with editing the translation and footnotes.

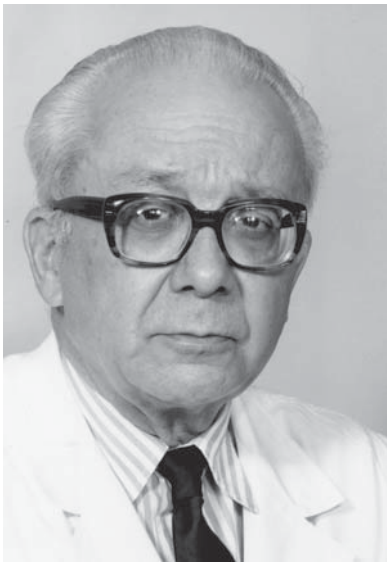

Figure A.1. Andrea Prader, 1919–2001.

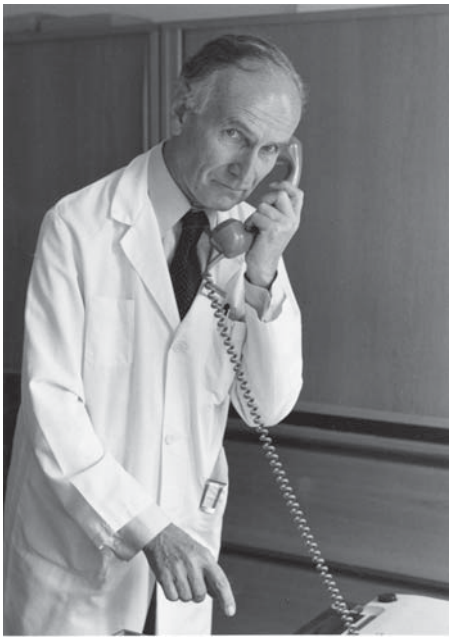

Figure A.2. Alexis Labhart, 1916–1994.

Figure A.3. Heinrich Willi, 1900–1971.

Ein Syndrom von Adipositas, Kleinwuchs, Kryptorchismus und Oligophrenie nach myatonieartigem Zustand im Neugeborenenalter*

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Es handelt sich um ein Syndrom von Kleinwuchs, Akromikrie, Adipositas und Imbezibillität, dem im Säuglingsalter regelmässig eine extrem schwere Muskelhypotonie vorausgegangen ist. Neben variablen kleineren degenerativen Merkmalen findet man beim Knaben regelmässig ein hypoplastisches, flach verstrichenes Skrotum mit inguinaler oder abdominaler Hodenretention.

Bisher haben wir dieses Syndrom bei 5 männlichen und 4 weiblichen Patienten beobachtet. Der älteste Patient ist 23jährig und die älteste Patientin 15jährig. Die übrigen sind 5–10 Jahre alt. Jüngere Patienten haben wir vorläufig nicht miteinbezogen, da sie noch nicht das volle klinische Bild erkennen lassen.

Alle diese Patienten hatten als Neugeborene eine extreme Muskelhypotonie, die sich darin äussert, dass die Kinder fast ganz bewegungslos und schlaff daliegen und weder schreien noch saugen können, so dass einen längere Hospitalisierung notwendig ist. Die Sehnenreflexe sind in diesem Zeitpunkt nicht oder nur schwach auslösbar. Die Diagnose lautet regelmässig "Lebensschwäche" oder "Myatonia congenita". Nach einigen Wochen macht sich wider Erwarten eine leichte Besserung bemerkbar, doch dauert es Monate, bis die Säuglinge schreien und sich kräftig bewegen können.

Wohl als Folge dieser sich nur ganz allmählich bessernden Muskelhypotonie lernen die Kinder erst mit 1 Jahr sitzen und erst mit 2 Jahren gehen. Während die Hypotonie und Adynamie zusehends bessern, tritt ungefähr um das 2. Jahr die Adipositas auf, und gleichzeitig werden der Wachstumsrückstand und die Oligophrenie deutlich bemerkbar.

Neurologisch findet man nach dem 5. Jahr noch eine geringfügige Muskelhypotonie und eine gewisse motorische Unbeholfenheit, jedoch ein normales Reflexbild. Der Kopf ist im Verhältnis zur Körpergrösse eher klein. Im Röntgenbild fehlen signifikante Sellaveränderungen. Die dreimal durchgeführte Luft-und Elektroencephalographie ergab unauffällige Befunde.

Stoffwechseluntersuchungen konnten leider nur bei der Hälfte der Patienten durchgeführt werden. Der Grundumsatz ist normal. Mit Ausnahme des ältesten Patienten, bei dem mit 17 Jahren ein Diabetes mellitus aufgetreten ist, ergibt die Prüfung des KH-, Elektrolyt- und Wasserstoffwechsels mit den üblichen Untersuchungen normale Befunde. Zeichen einer Hypothyreose fehlen. Die Pubertätsentwicklung scheint verzögert und unvollständig zu sein. Die 17-Ketosteroide

*Reprinted with permission from Prader, Labhart, and Willi, Ein syndrom von adipositas, kleinwuchs, kryptorchismus und oligophrenie nach myatonieartigem zustand im neugeborenenalter. *Schweizerische Medizinische Wochenschrift*. 1956;86:1260–1261.

der älteren Patienten sind auffallend tief. Die Gonadotropinausscheidung des 23-jährigen Patienten ist erhöht, d.h. es besteht wohl als Folge des Kryptorchismus ein hypergonadotroper Hypogonadismus. Der Vaginalabstrich des 15jährigen Mädchens zeigt eine deutliche Östrogenwirkung. Es scheint also keine Hypophyseninsuffizienz, sondern eher noch eine Hypothalamusstörung vorzuliegen. Bezüglich Ätiologie konnten wir bis jetzt weder für die Heredität noch für eine Embryopathie genügend Anhaltspunkte finden.

Zusammenfassend glauben wir, dass es sich um ein nicht so seltenes, gut abgegrenztes, einheitliches klinisches Syndrom handelt. Beim Säugling und Kleinkind erinnert es an die Myatonia congenita Oppenheim. Im Schulkindalter und später an die Dystrophia adiposogenitalis Fröhlich, an das Laurence-Moon-Biedl-Syndrom und an den hypophysären Zwergwuchs. Trotz mancher Ähnlichkeit lässt es sich aber von allen diesen Syndromen deutlich unterscheiden.

English translation:

A Syndrome Characterized by Obesity, Small Stature, Cryptorchidism and Oligophrenia Following a Myotonia-like Status in Infancy

A. Prader, A. Labhart and H. Willi
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The syndrome to be described is characterized by small stature, acromicria,[1] obesity and imbecility, regularly preceded by extreme muscle hypotonia in infancy. Apart from variable minor degenerative characteristics, one generally finds in boys a hypoplastic, flat scrotum with inguinal or abdominal retention of testicles.

So far, we have found this syndrome in 5 male and 4 female patients. The oldest patient is 23 years old, the oldest female patient 15 years. The others are between 5 and 10 years old. For the time being, we have not included younger patients, since they do not present the entire clinical picture.

As neonates, all these patients had suffered from extreme muscle hypotonia, leading to the children lying almost entirely motionless and floppy, not being able to either cry or suck, resulting in prolonged stays in hospitals. Hardly any tendon reflexes can be found at that stage. Typically, "Congenital Myotonia" or "Lebensschwäche"[2] were diagnosed. Unexpectedly, some improvement was generally seen after several weeks, but it takes months before the infants are able to cry and move with ease.

Probably as a consequence of the very slowly improving muscle hypotonia, the children are only able to sit at 1 year of age and to walk at the age of 2 years. While the hypotonia and adynamia[3] gradually improve, obesity sets in around the second year of life. At the same time, growth retardation and oligophrenia[4] become distinct.

The neurologic findings persist after age 5 years. Despite some motor clumsiness, reflexes are normal. The size of the head is rather small in relation to body height. X-rays do not reveal any disturbances in the

sella[5] area. The pneumo- and electro-encephalograms, performed three times, yielded normal results.

Metabolic tests could be conducted in only half of the patients but resulted in normal basal metabolic rates. Apart from the oldest patient, who had developed diabetes mellitus at the age of 17 years, tests of the carbohydrate, electrolyte and water metabolism yielded normal results when measured with conventional methods. No signs of hypothyroidism were found. Puberty seems to be delayed and incomplete. In the older patients, urinary 17-ketosteroid[6] excretion measurements were very low. The gonadotropin secretion of the 23-year-old patient was increased, the cryptorchidism probably led to a hypergonadotropic hypogonadism. The vaginal smear of the 15-year-old girl revealed a distinct effect of estrogens, which makes a hypothalamic disorder more likely than pituitary insufficiency. Regarding aetiology, we were not able to find sufficient evidence for heredity or for embryopathy.

In summary, we believe that this syndrome is not all that rare, clearly distinguishable, and well defined. Whereas in infants, it shows some similarity to amyotonia congenita of Oppenheim,[7] from school age on and later, it resembles Fröhlich's syndrome (adiposogenital dystrophy),[8] the Laurence-Moon-Biedl-Bardet syndrome,[9] and later, pituitary small stature.[10] Despite all the similarities, it can be clearly distinguished from the syndromes mentioned.

Footnotes to translation:

1. Acromicria: small hands and feet.
2. Lebensschwache: literally, life-weak (e.g., listless, moribund).
3. Adynamia: lack of physical movement.
4. Oligophrenia: a type of mental retardation leading to social incompetence; "feeble-mindedness."
5. Sella, *or* sella turcica: the area of the skull that contains the pituitary gland.
6. 17-ketosteroids: a urinary test, commonly used in the past as a marker for androgen production.
7. Amyotonia congenita of Oppenheim: a condition of severe, usually nonprogressive neonatal hypotonia described by Hermann Oppenheim in 1900. It appears that this is not an actual condition, but a description of signs and symptoms that are seen in a number of neonatal neuromuscular conditions, most notably spinal muscular atrophy.
8. Fröhlich's (adiposogenital dystrophy) syndrome is usually used to describe a condition in which adolescent boys are noted to have obesity and hypogonadotropic hypogonadism. The original case was due to a pituitary tumor and subsequent cases have involved a similar etiology, whereas other cases may have had a variety of conditions. This term is not commonly used in current medical practice.
9. Laurence-Moon-Biedl-Bardet syndrome was actually described by Bardet and Biedl in the 1920s and is currently known as Bardet-Biedl syndrome. It is characterized by obesity, short stature,

moderate mental retardation, retinal dystrophy, polydactyly, hypogonadism in males, and a variety of other abnormalities.
10. Pituitary short stature: e.g., growth hormone deficiency.

Commentary

The first description of the Prader-Willi syndrome—as it is now called—consisted of only 21 lines. The paragraphs above constitute the entire article—not just the abstract. The completeness and accuracy of this description and its pathophysiological implications meet with much admiration. Considering the limited methodological techniques of the time, this achievement becomes even more impressive. The description was so comprehensive that up until the 1980s, no substantial new knowledge was added.

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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:

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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, Immunodiagnostic Systems Ltd., Bolden, Tyne & Wear, UK]

Martin Ritzén, MD, Professor, Department of Pediatric Endocrinology, Karolinska Hospital, Stockholm, Sweden

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*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

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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.[1] 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.[2] Evidence is mounting that GH

Table B.1. Recommended Components of the Initial Visit to a Multidisciplinary Prader-Willi Syndrome Clinic

Evaluation
• **Confirmation of diagnosis, genetic counseling**
• **Complete examination**
• **Dietary evaluation and counseling**
• **Physical therapy evaluation (developmental, neuromuscular)**
• **Psychological evaluation and recommendations**
• **Educational evaluation and recommendations**
• **Initial discussion of growth hormone therapy and approval process**
Testing
• **DNA studies**
• **IGFBP-3, IGF-I, thyroid panel, lipid panel (other lab tests as clinically indicated)**
• **Screening for glucose intolerance if patient is obese (fasting glucose, glycated hemoglobin, oral glucose tolerance test, if indicated)**
• **Body composition analysis (DEXA, anthropometry, or other method)**
• **Psychological and/or educational testing**
• **Strength and endurance testing**

DEXA = dual-energy X-ray absorptiometry; IGF-I = insulin-like growth factor-I; IGFBP-3 = IGF binding protein-3.

deficiency may contribute not only to the abnormal growth pattern but also to the excess of body fat and the lean body mass deficit.[3,4] Growth hormone treatment of children with PWS normalizes linear growth,[5–10] promotes growth of lean body mass,[6–8,11,12] and decreases fat mass.[6–8,11,12] 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.[13] 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.[6] 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.[14] 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.[15] 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.[6] Thirty-five children received GH at a dose of $1\,mg/m^2/day$ 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,[7] and improvements in physical strength and agility.[8] 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.[7]

At baseline, 70% of subjects had mild to moderate scoliosis on spine films.[8] 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 24 U/m^2/week (~0.037 mg/kg/day) for a median of 4 years (range, 1.5 to 5.5 years).[9] 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,[12] 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.[17] 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.[18] 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[19] to study psychomotor development in 10 young, underweight children with PWS during the first year of GH treatment.[20] 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.[21] 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.[22] In addition, the increase in fasting insulin and insulin resistance seen in children with PWS during GH therapy is transient.[22] 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.[23] 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.[24]

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[25] of this study in 1997 and 5-year results[10] 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.[10] 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[27] 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.[28,29] Most agents either were ineffective or increased the occurrence of targeted symptoms; only three—haloperidol, thioridazine, and fluoxetine—were effective.[30] 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.[31] Other psychotropic drugs, such as the antipsychotic agent olanzapine and the anticonvulsant agent divalproex sodium, may have an effect.[31] 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.[31] 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.[1] 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.[26,32] 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.[26,32] 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.[33] 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.[34]

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.[35] 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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Appendix C

Growth Charts of Individuals with Prader-Willi Syndrome

Data from the United States

Data in Figures C.1 through C.5 are based on measurements of 71 Caucasian U.S. subjects with PWS between the ages of 0 and 24 years, including 42 males and 29 females, reported by Butler and Meaney. Under high-resolution chromosome analysis, 37 subjects had an apparent chromosome 15 deletion, 26 had normal-appearing chromosomes, and 8 had an unknown chromosome status. Approximately half of the subjects were on a calorie-restricted diet, and none were treated with growth hormone. No significant differences were found between those with a chromosome deletion and those with normal-appearing chromosomes, but there were significant variations by gender.

Data source: Butler MG, Meaney FJ. Standards for selected anthropometric measurements in Prader-Willi syndrome. *Pediatrics*, 1991:88(4);853–860. Reproduced by permission of *Pediatrics*, 1991:88;853–858. (Charts were modified by Dr. Merlin Butler to add standard measure equivalents to the original metric units.)

Data from Germany

Data in Figures C.6 and C.7 are based on measurements of 100 subjects of German descent between the ages of 0 and 20 years, including 51 males and 49 females, reported by Hauffa et al. All subjects had genetically confirmed PWS by molecular genetics testing; 76 had deletions, 14 had maternal uniparental disomy, 3 had imprinting mutations, and 7 were of undetermined molecular class. None of the subjects had received a growth-promoting therapy. In comparison with the U.S. data described above, the researchers found that "Height centile curves of the German patients fall in the tall range of standards derived from American patients . . . mainly due to an elevation of the lower centile ranges in both sexes." They also found that after age 14 "German girls with PWS are heavier than their American counterparts."

Data source: Dr. Berthold P. Hauffa provided combination height and weight charts based on PWS data reported in Hauffa BP, Schlippe G, Roos M, Gillessen-Kaesbach G, Gasser T. "Spontaneous growth in German children and adolescents with genetically confirmed Prader-Willi syndrome." *Acta Paediatrica,* 2000:89:1302–1311. These modified clinical charts were prepared by Pharmacia Corporation, substituting German reference data for the Dutch reference data in the original article. Reprinted with English labels by permission of Pharmacia Corporation.

Data from Japan

Data in Figures C.8 through C.15 are based on measurements of 252 Japanese individuals with PWS between the ages of 0 and 24 years, including 153 males and 99 females, reported by Nagai et al. The subjects were diagnosed with PWS by clinical, cytogenetic, and/or molecular genetic methods; 198 were found to have a chromosome 15q abnormality (deletion), 26 had maternal uniparental disomy, and in 28 no chromosome analysis was available. Approximately one third of the subjects were on a calorie-restricted diet. The researchers found that "Growth patterns are not different between Japanese and Caucasian children with the syndrome" but that "the degree of overweight appears much more severe in Caucasians."

Data source: Nagai T, Matsuo N, Kayanuma Y, et al., Standard growth curves for Japanese patients with Prader-Willi syndrome," *American Journal of Medical Genetics,* 2000:95;130–134. Original growth charts from this report, courtesy of Dr. Toshiro Nagai, are reprinted with permission of Wiley-Liss, Inc., a subsidiary of John Wiley & Sons, Inc.

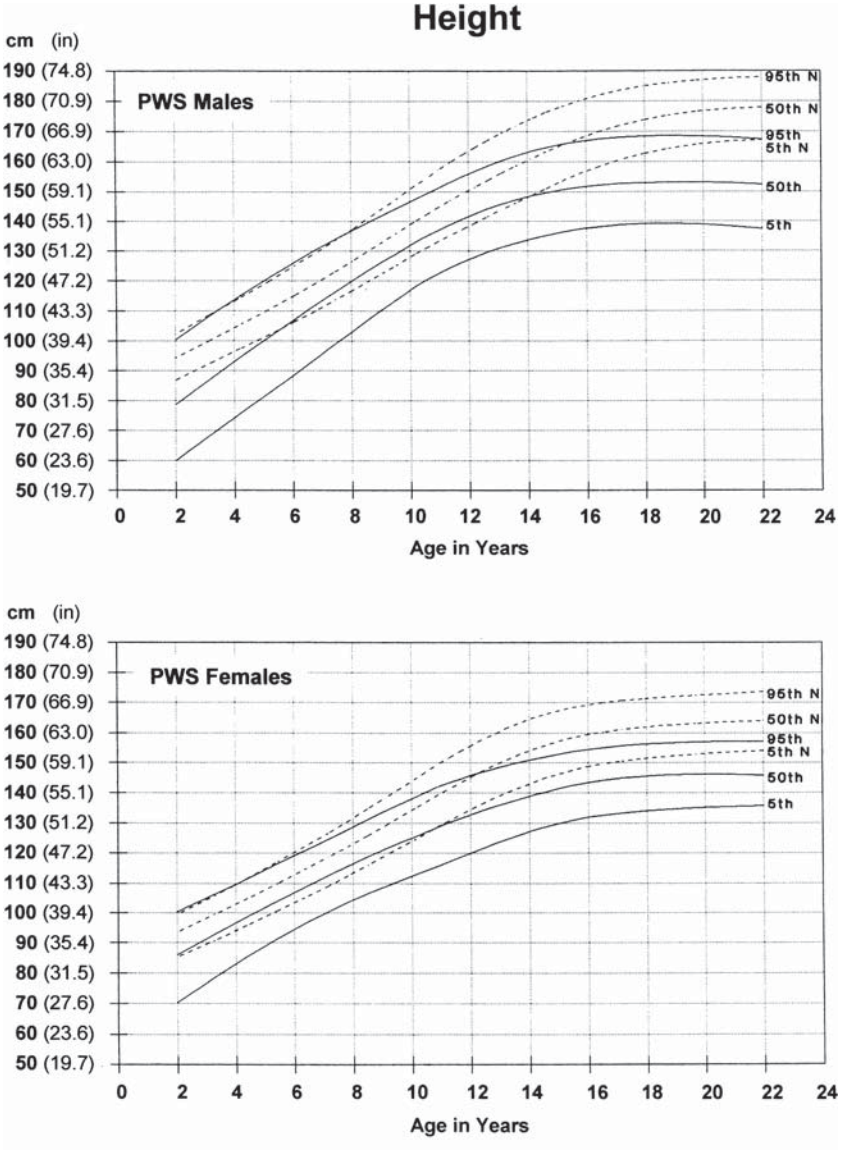

Figure C.1. Data from USA. Standardized curves for height of Prader-Willi syndrome (PWS) male and female patients (solid line) and healthy individuals (broken line). Modified from Butler and Meaney, 1991. Reproduced by permission of *Pediatrics*, Vol. 88, p. 854, Copyright © 1991.

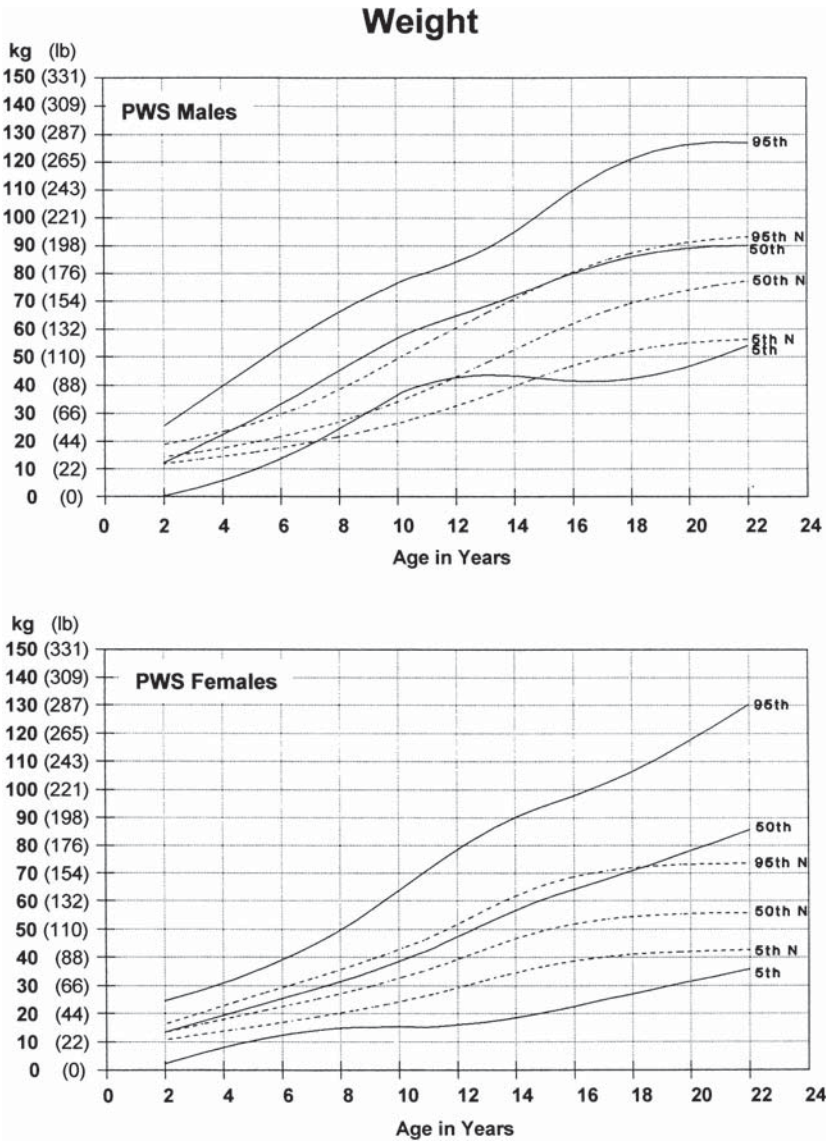

Figure C.2. Data from USA. Standardized curves for weight of Prader-Willi syndrome (PWS) male and female patients (solid line) and healthy individuals (broken line). Modified from Butler and Meaney, 1991. Reproduced by permission of *Pediatrics*, Vol. 88, p. 853, Copyright © 1991.

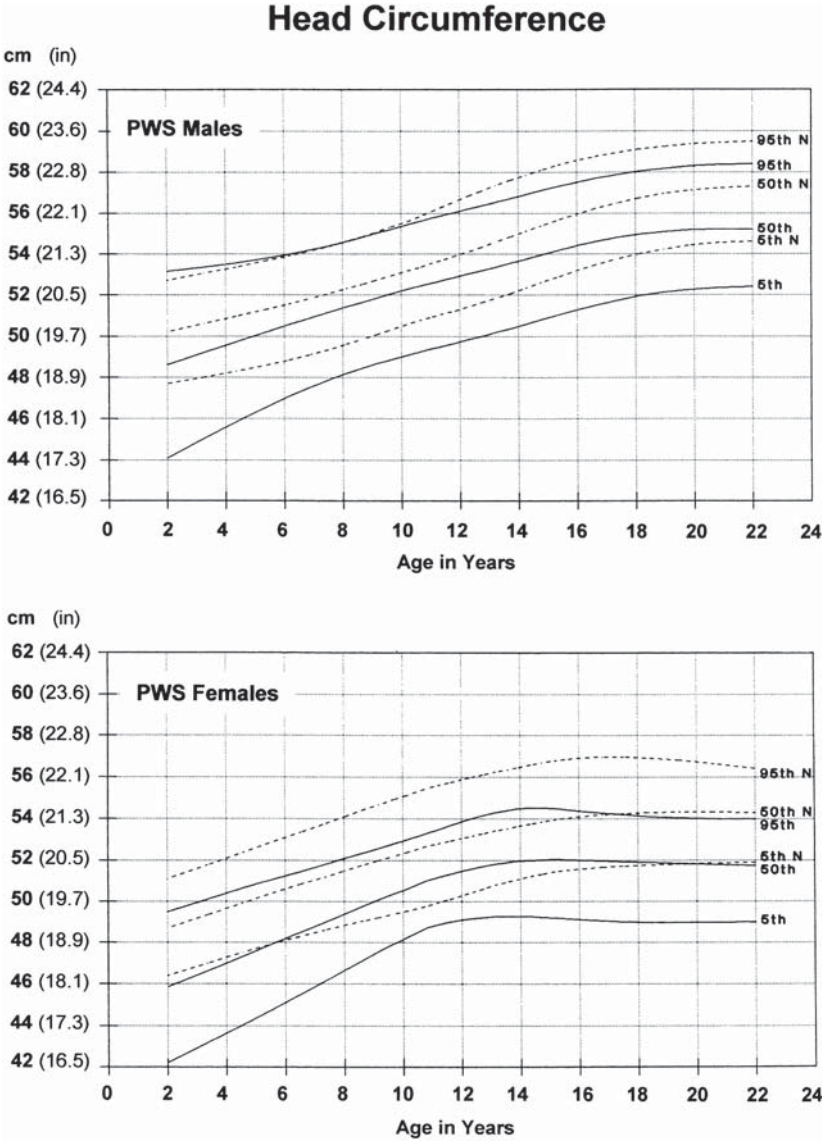

Figure C.3. Data from USA. Standardized curves for head circumference of Prader-Willi syndrome (PWS) male and female patients (solid line) and healthy individuals (broken line). Modified from Butler and Meaney, 1991. Reproduced by permission of *Pediatrics*, Vol. 88, p. 855, Copyright © 1991.

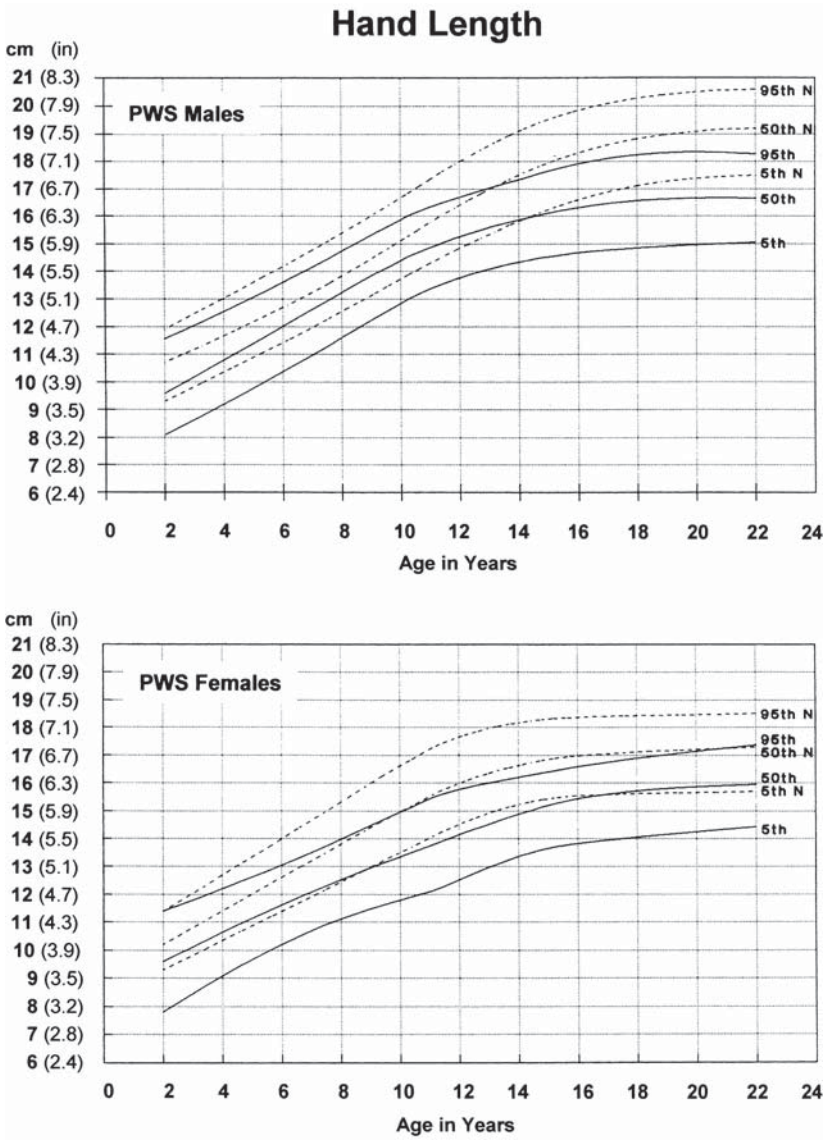

Figure C.4. Data from USA. Standardized curves for hand length of Prader-Willi syndrome (PWS) male and female patients (solid line) and healthy individuals (broken line). Modified from Butler and Meaney, 1991. Reproduced by permission of *Pediatrics*, Vol. 88, p. 856, Copyright © 1991.

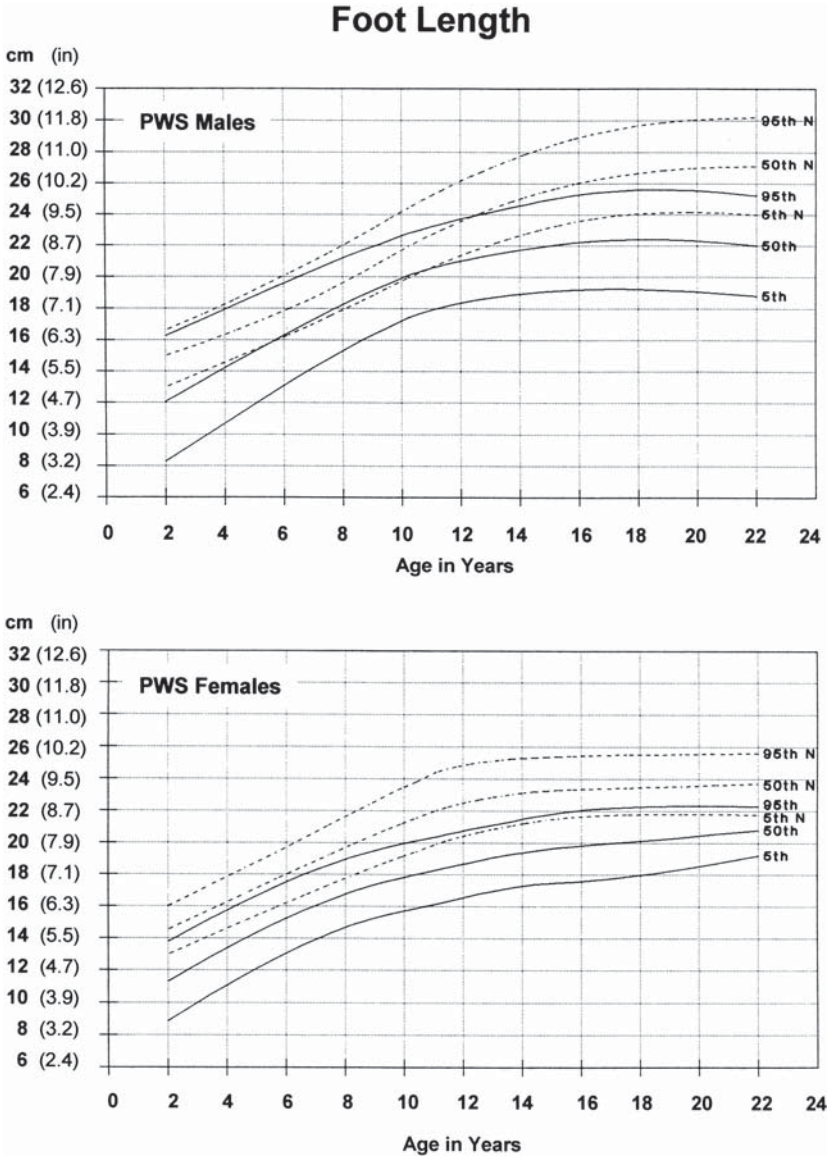

Figure C.5. Data from USA. Standardized curves for foot length of Prader-Willi syndrome (PWS) male and female patients (solid line) and healthy individuals (broken line). Modified from Butler and Meaney, 1991. Reproduced by permission of *Pediatrics*, Vol. 88, p. 858, Copyright © 1991.

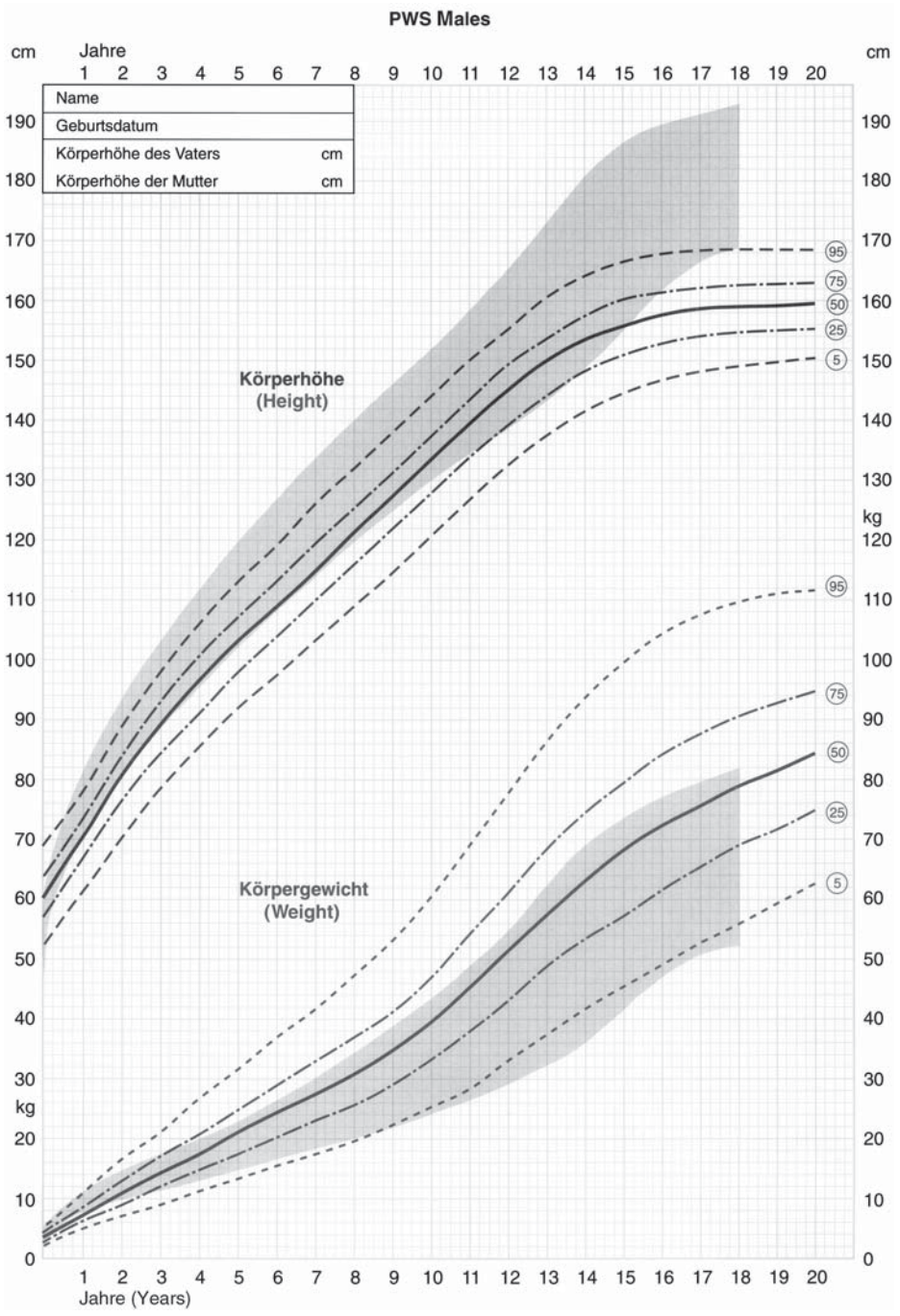

Figure C.6. Data from Germany. Centile curves (5th, 25th, 50th, 75th, 95th centile) for length/height (top) and for weight (bottom) of male German PWS patients, compared with reference growth standards of normal children (shaded area representing the 3rd to 97th centile range). Modified clinical chart based on Hauffa et al., *Acta Paediatrica*, 2000, Vol. 89, pp. 1302–1311. Reprinted with permission from Pharmacia Corp. Chart courtesy of Dr. Berthold P. Hauffa.

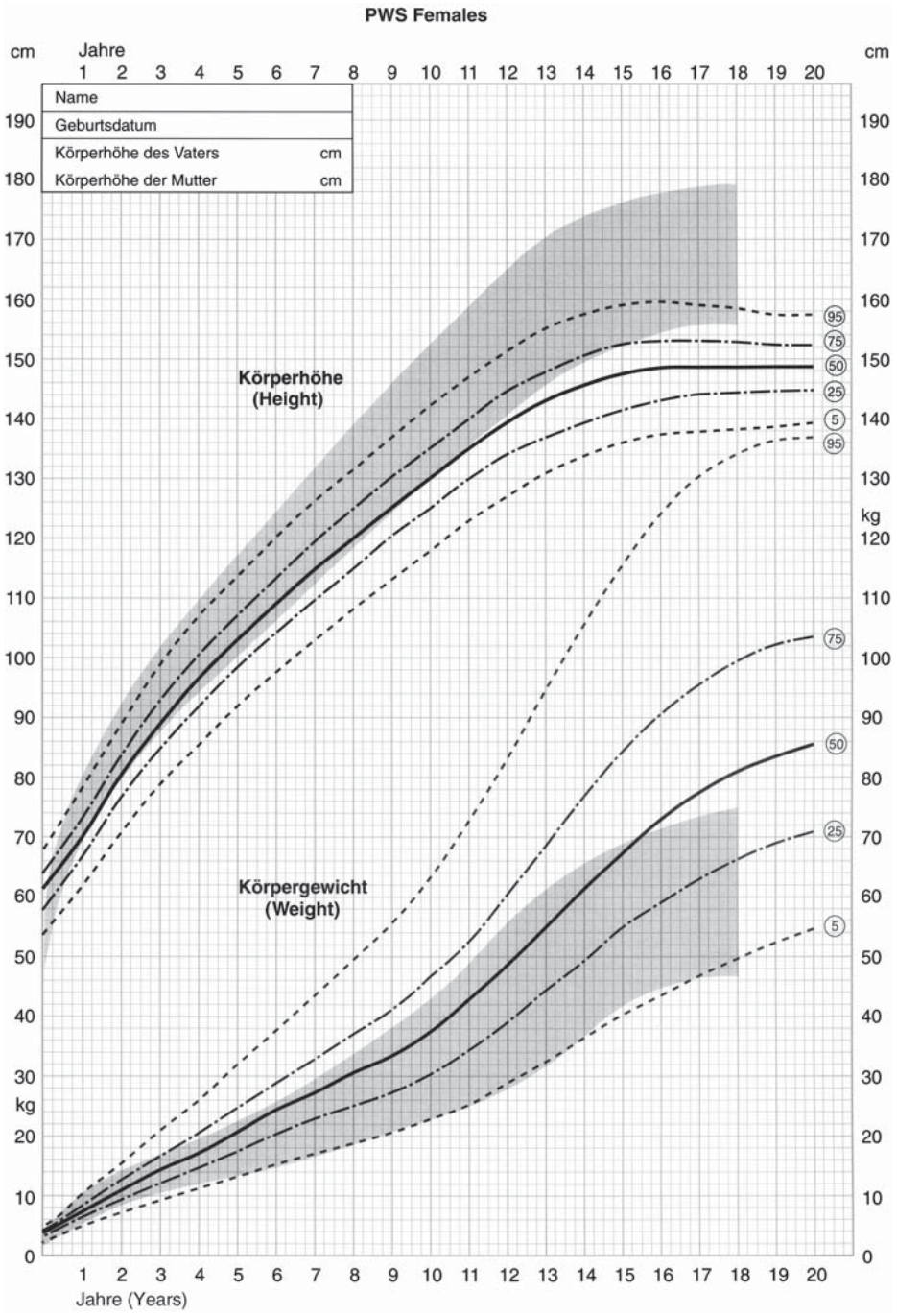

Figure C.7. Data from Germany. Centile curves (5th, 25th, 50th, 75th, 95th centile) for length/height (top) and for weight (bottom) of female German PWS patients, compared with the reference growth standards of normal children (shaded area representing the 3rd to 97th centile range). Modified clinical chart based on Hauffa et al., *Acta Paediatrica*, 2000, Vol. 89, pp. 1302–1311. Reprinted with permission from Pharmacia Corp. Chart courtesy of Dr. Berthold P. Hauffa.

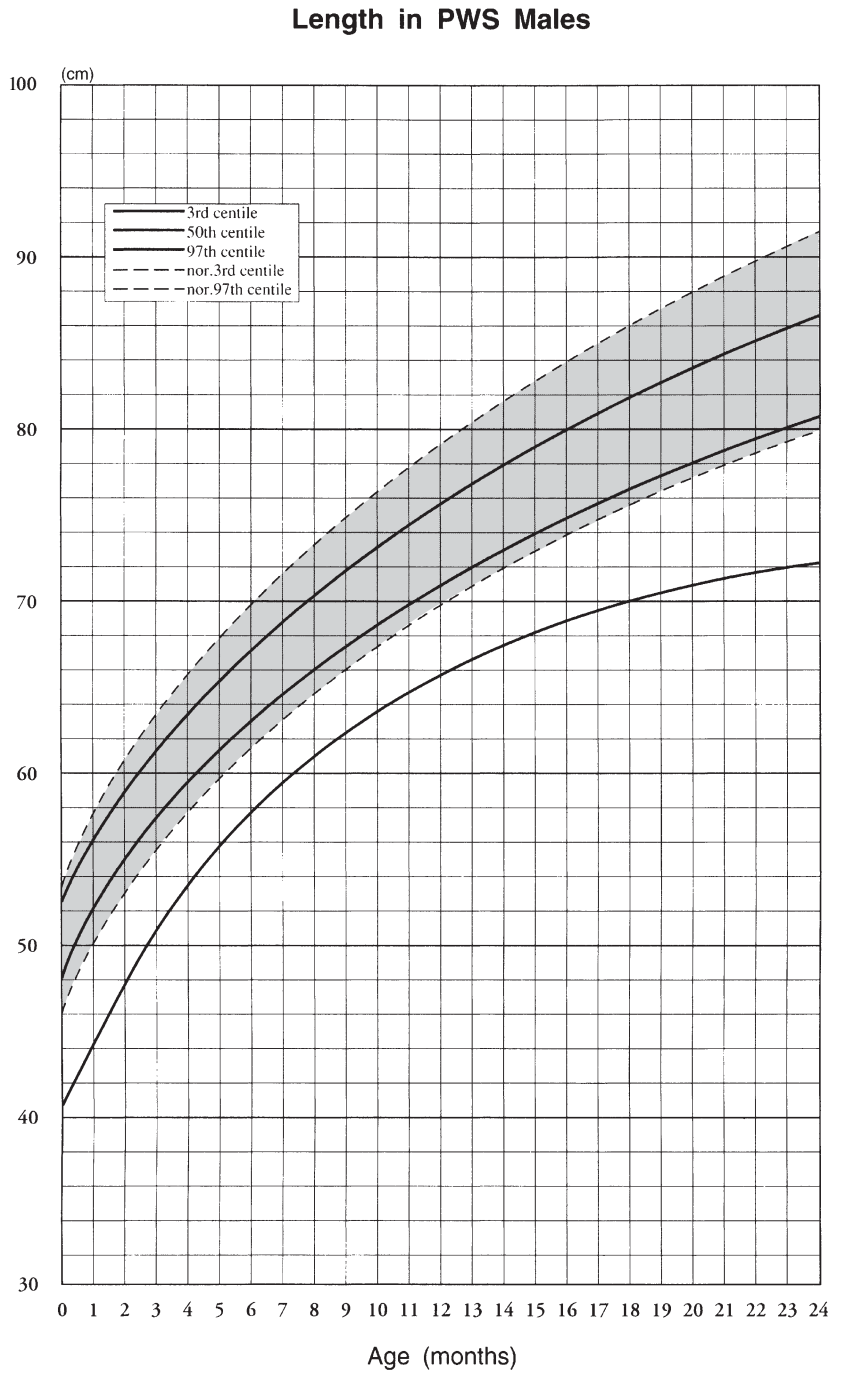

Figure C.8. Data from Japan. Body length of male Japanese PWS patients from birth to age 24 months. Solid lines show 3rd, 50th, and 97th centile values for PWS patients, and dotted lines 3rd and 97th centile values for normal children. From Nagai et al., *American Journal of Medical Genetics*, Vol. 95, p. 131, Copyright © 2000. Reprinted with permission of Wiley-Liss, Inc., a subsidiary of John Wiley & Sons, Inc. Chart courtesy of Dr. Toshiro Nagai.

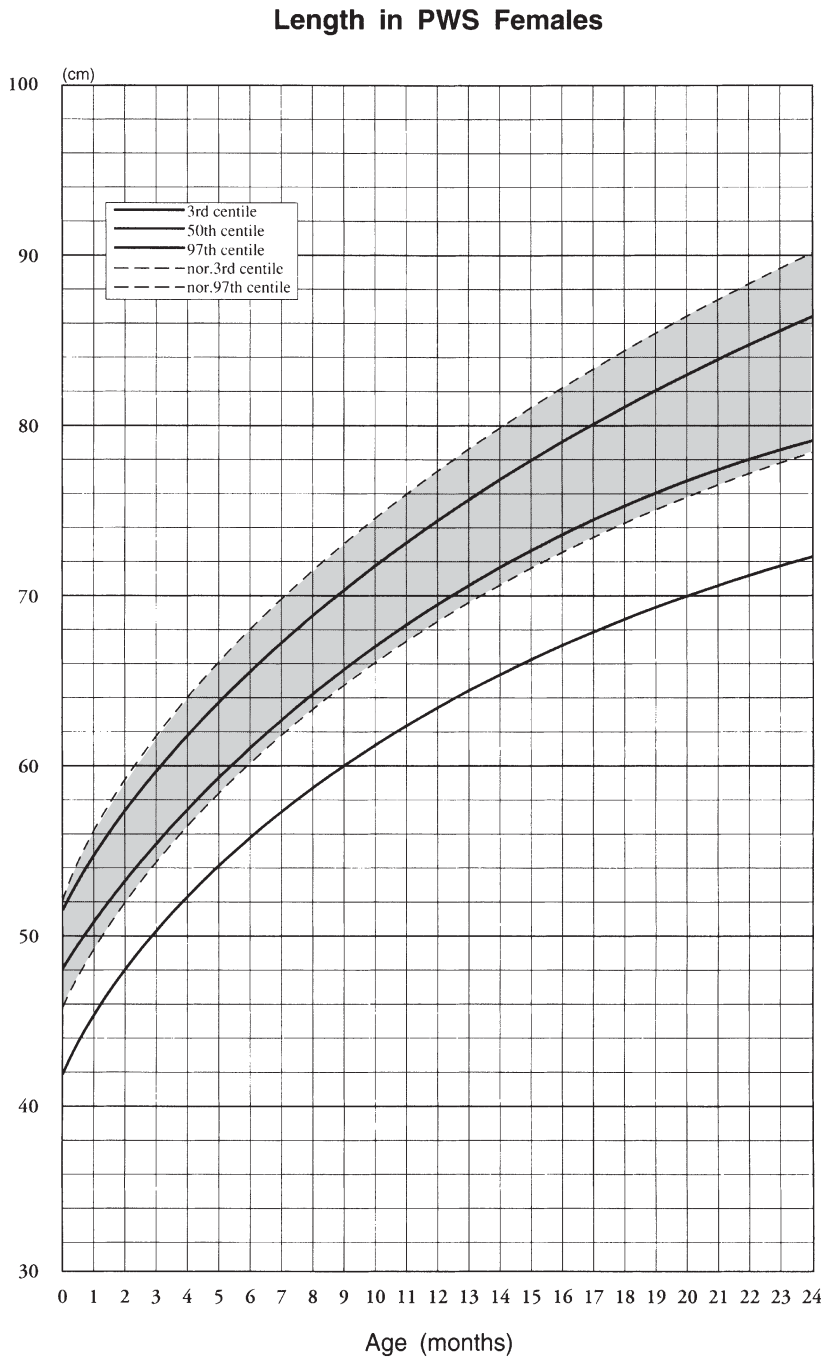

Figure C.9. Data from Japan. Body length of female Japanese PWS patients from birth to age 24 months. Solid lines show 3rd, 50th, and 97th centile values for PWS patients, and dotted lines 3rd and 97th centile values for normal children. From Nagai et al., *American Journal of Medical Genetics*, Vol. 95, p. 131, Copyright © 2000. Reprinted with permission of Wiley-Liss, Inc., a subsidiary of John Wiley & Sons, Inc. Chart courtesy of Dr. Toshiro Nagai.

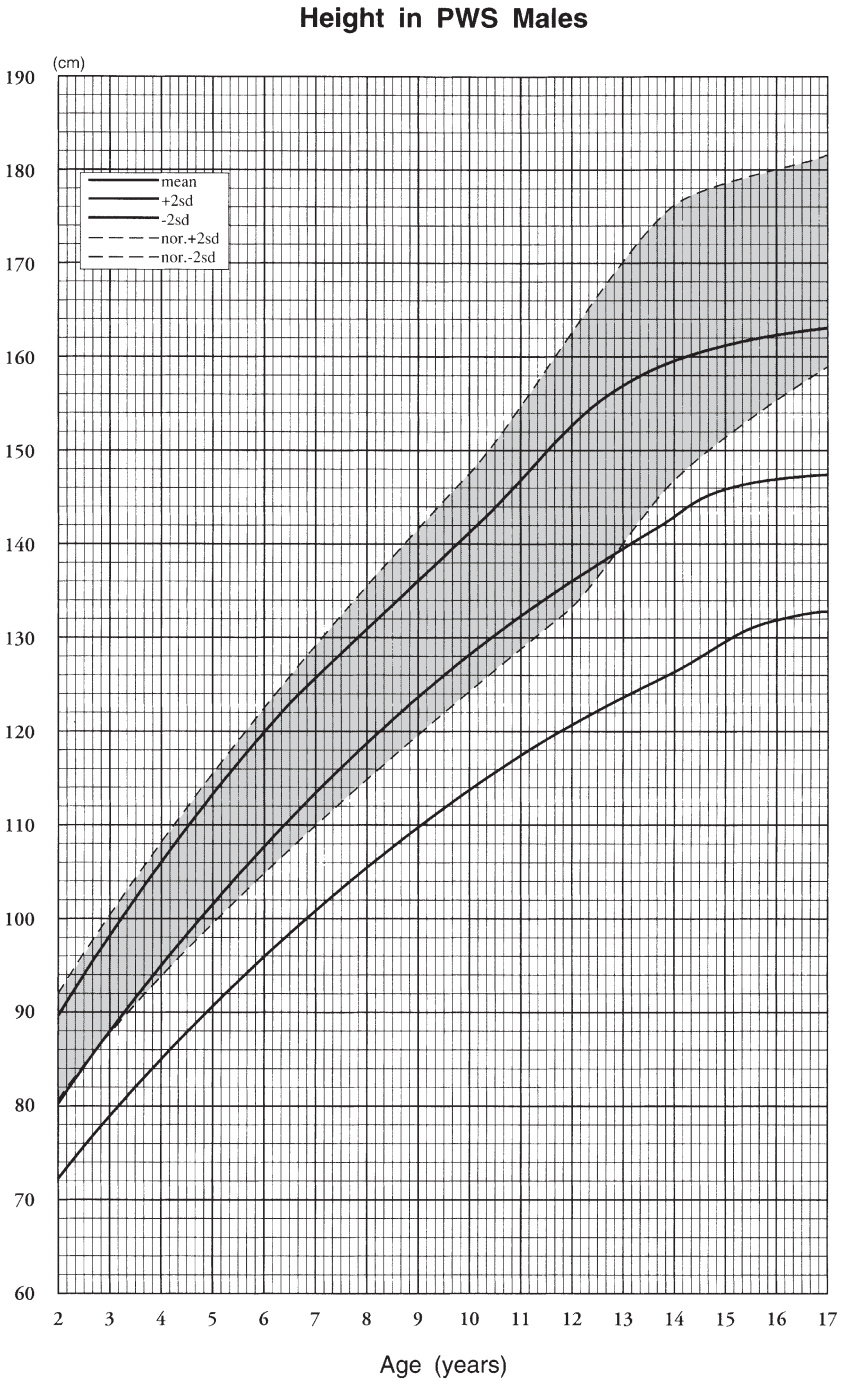

Figure C.10. Data from Japan. Height of male Japanese PWS patients from ages 2 to 17 years. Solid lines show 3rd, 50th, and 97th centile values for PWS patients, and dotted lines 3rd and 97th centile values for normal children. From Nagai et al., *American Journal of Medical Genetics*, Vol. 95, p. 132, Copyright © 2000. Reprinted with permission of Wiley-Liss, Inc., a subsidiary of John Wiley & Sons, Inc. Chart courtesy of Dr. Toshiro Nagai.

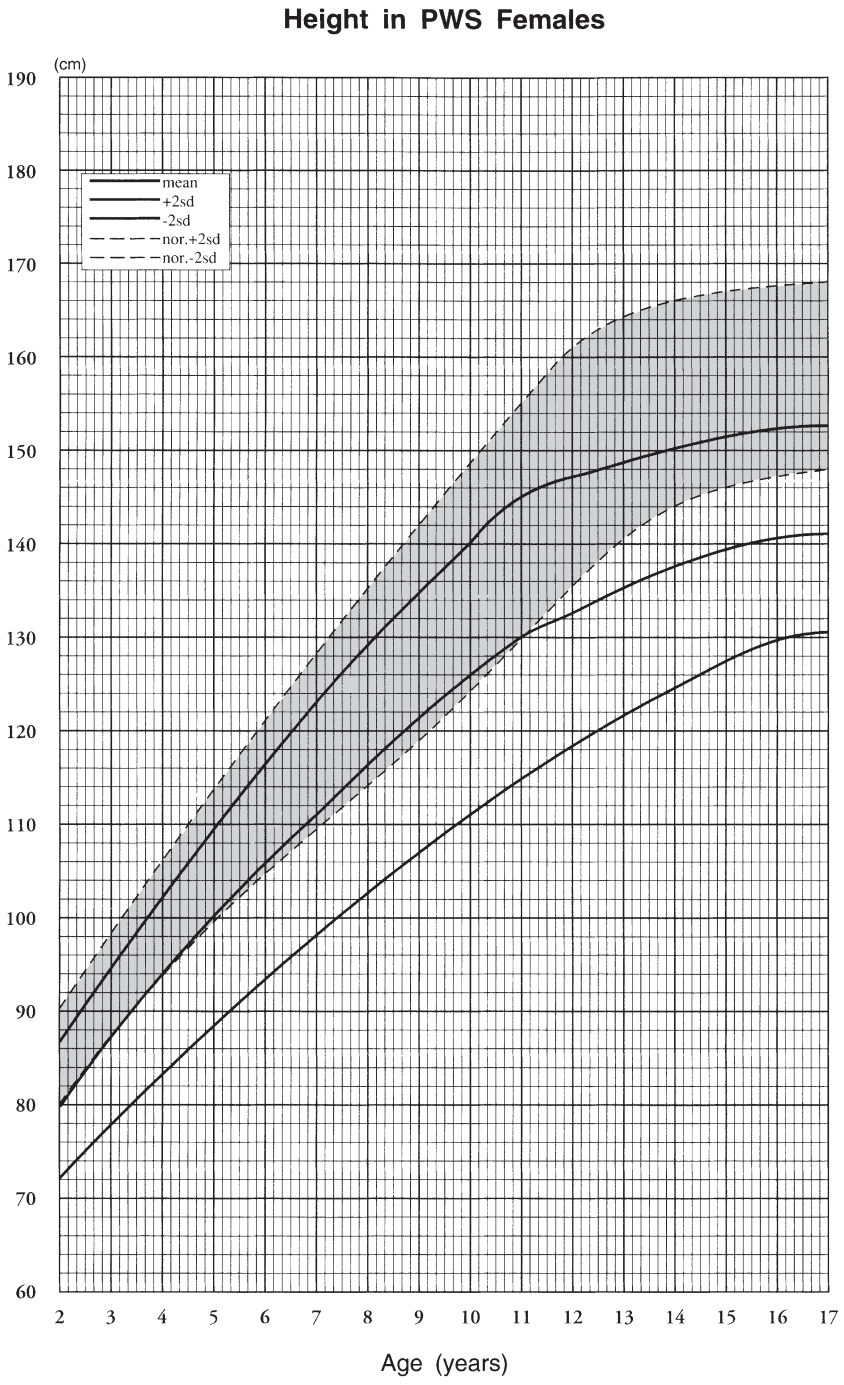

Figure C.11. Data from Japan. Height of female Japanese PWS patients from ages 2 to 17 years. Solid lines show 3rd, 50th, and 97th centile values for PWS patients, and dotted lines 3rd and 97th centile values for normal children. From Nagai et al., *American Journal of Medical Genetics*, Vol. 95, p. 132, Copyright © 2000. Reprinted with permission of Wiley-Liss, Inc., a subsidiary of John Wiley & Sons, Inc. Chart courtesy of Dr. Toshiro Nagai.

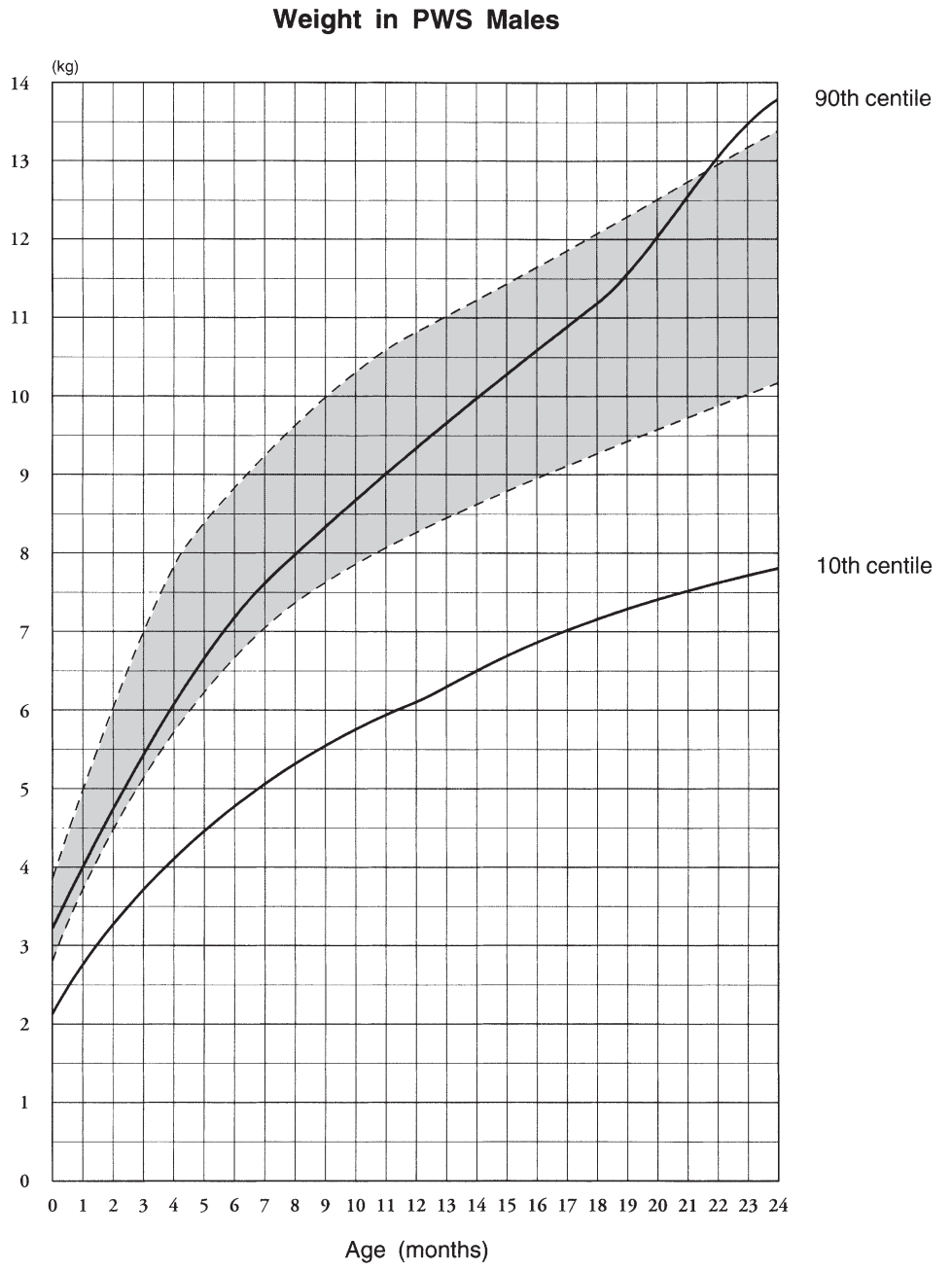

Figure C.12. Data from Japan. Body weight of male Japanese PWS patients from birth to age 24 months. Solid lines show 3rd, 50th, and 97th centile values for PWS patients, and dotted lines 3rd and 97th centile values for normal children. From Nagai et al., *American Journal of Medical Genetics*, Vol. 95, p. 133, Copyright © 2000. Reprinted with permission of Wiley-Liss, Inc., a subsidiary of John Wiley & Sons, Inc. Chart courtesy of Dr. Toshiro Nagai.

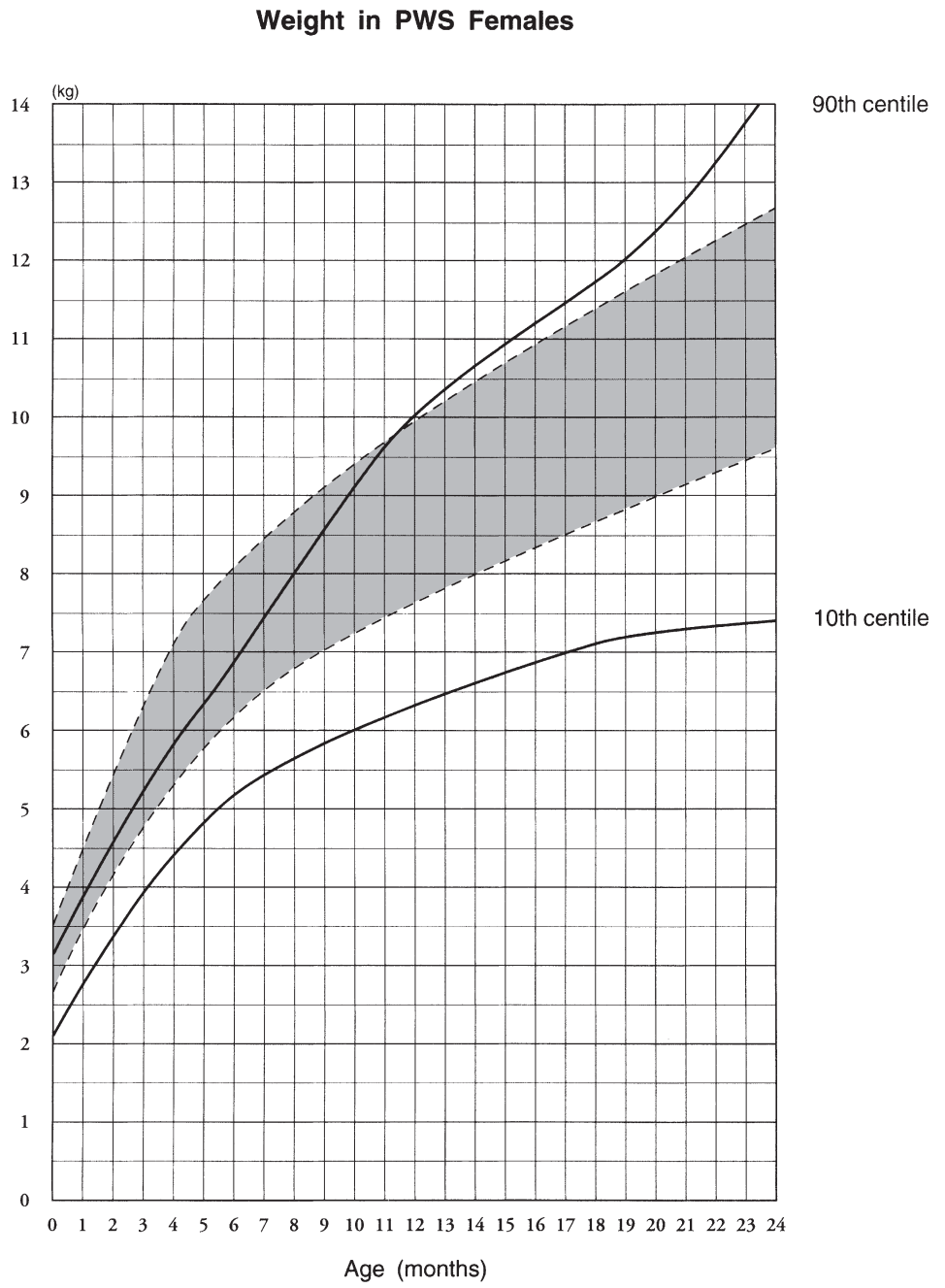

Figure C.13. Japanese Data. Body weight of female Japanese PWS patients from birth to age 24 months. Solid lines show 3rd, 50th, and 97th centile values for PWS patients, and dotted lines 3rd and 97th centile values for normal children. From Nagai et al., *American Journal of Medical Genetics*, Vol. 95, p. 133, Copyright © 2000. Reprinted with permission of Wiley-Liss, Inc., a subsidiary of John Wiley & Sons, Inc. Chart courtesy of Dr. Toshiro Nagai.

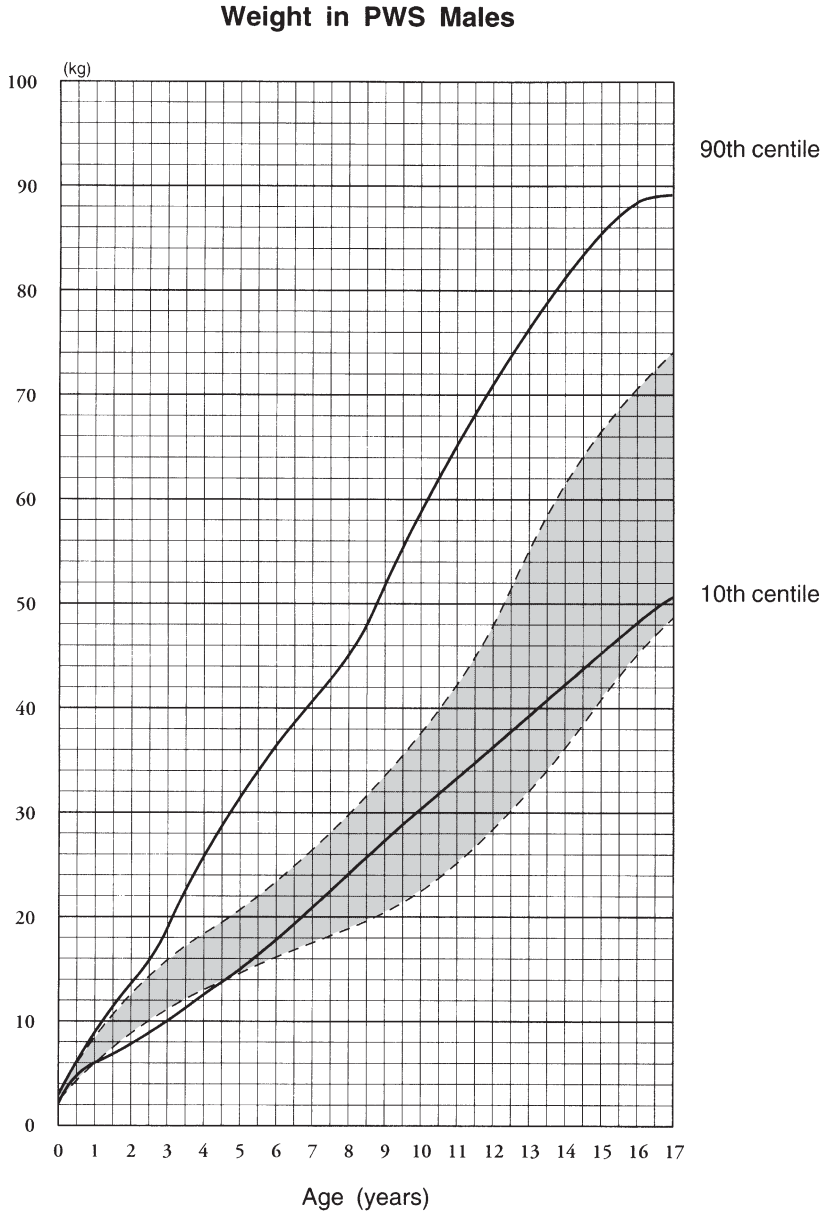

Figure C.14. Japanese Data. Body weight of male Japanese PWS patients from ages 2 to 17 years. Solid lines show 3rd, 50th, and 97th centile values for PWS patients, and dotted lines 3rd and 97th centile values for normal children. From Nagai et al., *American Journal of Medical Genetics*, Vol. 95, p. 133, Copyright © 2000. Reprinted with permission of Wiley-Liss, Inc., a subsidiary of John Wiley & Sons, Inc. Chart courtesy of Dr. Toshiro Nagai.

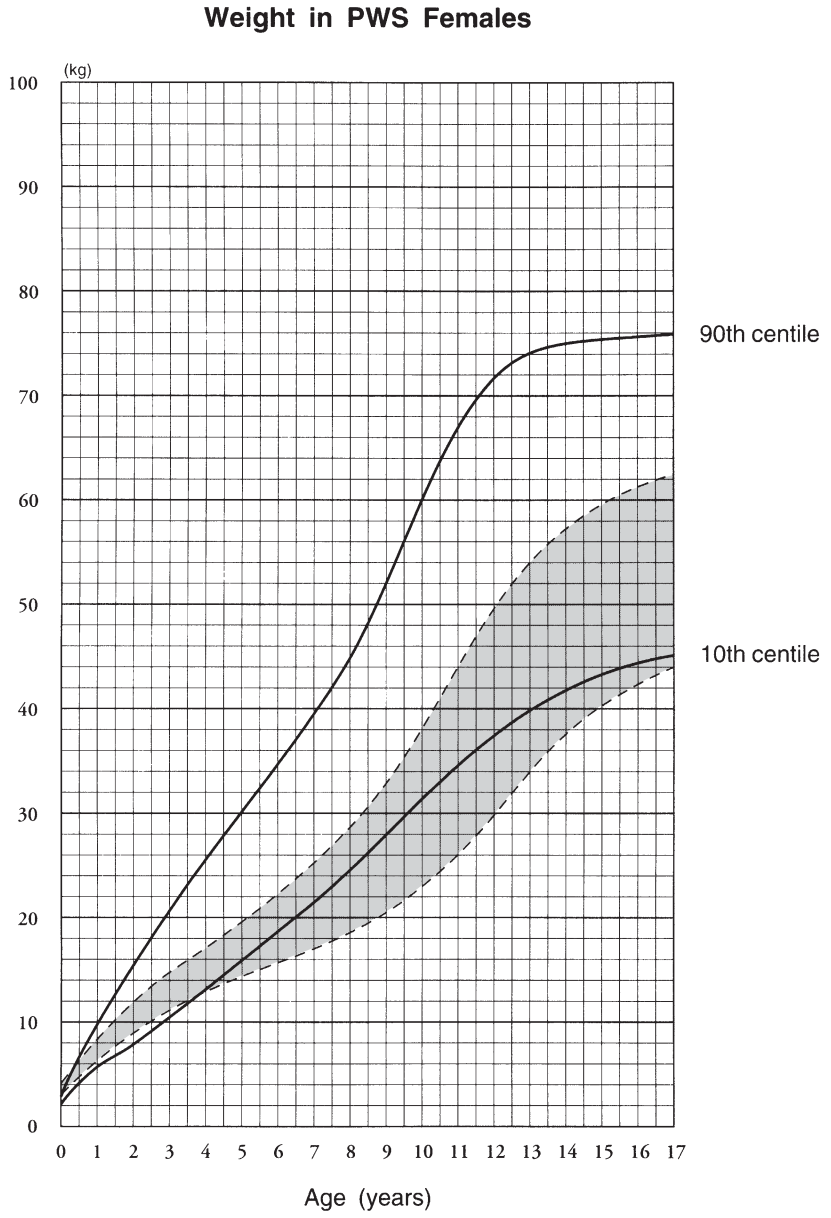

Figure C.15. Japanese Data. Body weight of female Japanese PWS patients from ages 2 to 17 years. Solid lines show 3rd, 50th, and 97th centile values for PWS patients, and dotted lines 3rd and 97th centile values for normal children. From Nagai et al., *American Journal of Medical Genetics*, Vol. 95, p. 133, Copyright © 2000. Reprinted with permission of Wiley-Liss, Inc., a subsidiary of John Wiley & Sons, Inc. Chart courtesy of Dr. Toshiro Nagai.

Appendix D

Eligibility for U.S. Social Security and SSI Benefits for Individuals with Prader-Willi Syndrome

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If your child suffers from a chronic condition such as Prader-Willi syndrome, you may have concerns about affording the care he currently needs and his well-being when you are no longer able to support him. If your child is sufficiently disabled and will be unable to work, you need more information about the disability benefits programs administered by the U.S. Social Security Administration (SSA).

The Social Security Administration administers two types of programs for disabled individuals: Social Security Disability Insurance (SSDI), also known as Title II and DIB, and Supplemental Security Income, also known as SSI and Title XVI. Although they have the same definition of disability, there are different requirements for each benefit program.

Social Security Disability Insurance is paid to adults who become disabled and who have a sufficient work history. SSDI also provides income for their dependents. Dependents include their minor children, disabled adult children, and sometimes their spouse. Medicare coverage is available after the disabled individual has received benefits for 2 years. The other benefit, SSI, is means-tested. These benefits are paid to disabled adults who have limited income and resources (most adults with Prader-Willi syndrome receive SSI) and to disabled children whose parents have limited income and resources. Due to the "deeming" of parents' income and resources to minor children, children can receive SSI benefits only if their parents have limited income and resources. Medicaid coverage is available upon receipt of SSI benefits. Many people receive benefits under both the SSI and Medicaid programs. There are special rules for SSI eligibility for noncitizens. If you are not a U.S. citizen, contact your attorney or SSA for more information.

An important benefit to be aware of is called Disabled Adult Children's (DAC) benefits. If a child is unmarried and his disability has

continued uninterrupted since before his 22nd birthday, and one of his parents is either retired, disabled, or has died after working enough quarters to qualify as insured, he may be eligible for Social Security disability benefits. Disabled Adult Children's benefits are available to your child even if he or she has never worked and can be used to support a disabled individual whose parents are no longer able to do so. Although these benefits are called "children's" benefits, they are paid to the adult child of a former wage earner. When a recipient of DAC benefits marries, these benefits will end. If you think your child may be eligible for this benefit, you should contact the Social Security Administration for an application. Visit a local office or call 1-800-772-1213. For a referral to a private attorney who is familiar with these benefits, you can call the National Organization of Social Security Claimants' Representatives at 1-800-431-2804.

Determining Eligibility

Social Security Disability Insurance benefits are available to disabled workers who meet two conditions: (1) they are too disabled to work at *any* job, not just the jobs which they held in the past; and (2) through their employment, they have contributed enough FICA tax over the years to be covered. In general, workers who have worked at least 5 out of the 10 years just before the disability began are covered; the rules are different for workers under age 30. An individual's wage history determines the monthly benefit amount.

Remember, even an individual who has not worked, but whose disability began before age 22, may be eligible for Social Security disability benefits, as a Disabled Adult Child.

Supplemental Security Income (SSI) benefits are available to disabled individuals whose income and resources are very limited. Generally, to be eligible for SSI benefits, an individual may have no more than $2,000 in resources ($3,000 for a couple) and income that is less than the SSI benefit amount ($579 per month for an individual and $869 for a couple in January 2005). The income levels change slightly each year. There are several items, such as a primary residence, car, and certain income, that SSA will not count. Income and resources from a spouse or the parents of a minor child are deemed available to the claimant. Parents' income will be deemed to a minor child even if he or she resides at a school, if the parent has parental control (guardianship) over the child.

Claimants who are eligible for Social Security disability benefits but whose payment amount is very low may also be eligible for SSI benefits.

Who Is "Disabled"?

Eligibility for benefits depends on a child's limitations resulting from physical, mental, and behavioral impairments. SSA decides whether a child has been, or is expected to be, disabled for at least 12 months. The

SSA definition of disability for a child is: "An individual under the age of 18 shall be considered disabled for purposes of this title if that individual had a medically determinable physical or mental impairment which results in marked and severe functional limitations, and which can be expected to result in death or which has lasted or can be expected to last for a continuous period of not less than 12 months."

Eligibility for disability benefits depends on the limitations an individual has as a result of *both* physical and mental impairments. For example, SSA will consider the effects of obesity on the individual's heart and ability to walk, as well as other conditions it may cause, such as diabetes or sleep apnea. SSA will also consider mental limitations, including IQ scores and limitations in social functioning and activities of daily living and maladaptive behavior. For example, temper tantrums, obsessive-compulsive behavior, frustration, and need for routine can limit available jobs and can be a "marked and severe functional limitation" in a child's case.

SSA follows a Sequential Evaluation Process to determine whether a claimant meets the disability criteria. For children, the sequential evaluation is a three-step process:

1. Is the child working?
2. Does the child have a medically determinable impairment or combination of impairments that is severe?
3. Does the child's impairment meet or medically equal the requirements of a listed impairment; or are the functional limitations caused by the impairment(s) the same as the disabling functional limitations of any listing, and therefore, functionally equivalent to that listing?

If the child is not working, SSA will compare the child's condition to its criteria in the "Listings of Impairments." There are several different listings under which an individual with Prader-Willi syndrome may be evaluated.

One listing that SSA may refer to is section 110.00, Multiple Body Systems. Those impairments that SSA classifies as "multiple body systems" are "life-threatening catastrophic congenital abnormalities and other serious hereditary, congenital, or acquired disorders that usually affect two or more body systems" and are expected to either produce long-term significant interference with age-appropriate major daily activities or result in early death. SSA will find a child disabled who suffers from multiple body dysfunction due to any confirmed hereditary, congenital, or acquired condition with either persistent motor dysfunction; significant interference with communication due to speech, hearing, or visual impairments; or mental, growth, or cardiac impairments.

SSA may also evaluate a child with Prader-Willi syndrome under the listings for mental disorders, section 112.00. These listings provide specific requirements for each age group. The conditions in this section that are most likely to be present in a child with Prader-Willi syndrome include: organic mental disorders (112.02); mood disorders (112.04); mental retardation (112.05); anxiety disorders (112.06); somatoform, eating, and tic disorders (112.07); pervasive developmental disorders

(112.10); or developmental and emotional disorders of newborn and younger infants (112.12).

If your child's condition precisely meets any of these criteria, SSA will find that he is disabled. But meeting these criteria is not the only way to qualify for benefits. Even if your minor child does not have the exact test results required, SSA will continue to evaluate the claim by determining whether his or her impairments cause the same type of limitations as any of the listings (medically or functionally equal the listing). Keep in mind that your child's disability can be based on a combination of several impairments that may not be disabling when considered separately, but when evaluated together show that he cannot work.

Functional equivalence is shown when the impairment or a combination of impairments causes the same disabling functional limitations as those of a listed impairment. SSA recognizes that some impairments or combination of impairments can be just as disabling even if the impairment itself is not the same as a listed impairment. SSA will also consider other factors such as the effect of medications, or the effects of structured settings, and school attendance. SSA may recognize that your child functions well in his supportive, special class in school or with the family and friends he knows, but may not be able to function well in an unknown setting or without constant support and supervision.

Although there is no longer a listing for obesity, SSA will also rely on the guidance found in Social Security Ruling 02-1p, which explains how obesity can affect an individual's musculoskeletal, cardiovascular, and respiratory systems.

Remember that SSA reviews and sometimes changes the specific requirements of any listing. Be sure you are relying on the current listing when gathering the necessary medical evidence.

SSA will consider the combined effects of all impairments to determine if the child is disabled under this category. Although an individual's physical or mental impairments considered independently may not be found to be disabling, when SSA considers the combined effect of all impairments, the condition can be functionally equal to a listed impairment.

Claimants over 18 years old are evaluated under adult standards. The adult listing for Multiple Body Systems (Section 10.00) is currently limited to Down syndrome, but this listing explains that SSA will evaluate "other chromosomal abnormalities [that] produce a pattern of multiple impairments but manifest in a wide range of impairment severity . . . under the affected body system." An adult can also be evaluated under the adult listings for Mental Disorders (Section 12.00) and Social Security Ruling 02-1p. As in a child's claim, SSA will consider the combined effect of all impairments on the individual's ability to work.

An adult whose condition does not meet the exact criteria, or who does not have the exact test results required may still be found disabled. SSA will continue to evaluate the claim by considering vocational factors (age, educational background, and work history) along with physical and mental residual functional capacities to decide

whether a claimant is disabled or whether there are jobs that he can do.

What Can You Do to Help Show SSA That You Are Disabled?

SSA will rely on the results of medical tests to determine whether your child can be found disabled, so it is important that he or she has been properly examined by a doctor. SSA wants to see that a doctor has laboratory tests, including chromosomal analysis, where appropriate, and has diagnosed your child with Prader-Willi syndrome. In addition to medical tests, SSA will consider the opinions of the treating physicians, the child's parents, and teacher's notations in school records. Both adults and children can assist their claim by keeping a diary documenting symptoms and how these symptoms affect the ability to function during a typical day.

You can also provide the Administrative Law Judge (ALJ) with medical information about Prader-Willi syndrome *before your hearing*, so the ALJ can be familiar with the nature of the condition. The Prader-Willi Syndrome Association has valuable information that can be provided to the ALJ. (See Appendix F.)

Applying for Benefits

Application forms for disability benefits from the Social Security Administration are obtainable by calling 1-800-772-1213. When the forms are complete, application for both Social Security Disability Insurance and SSI benefits can be filed at any Social Security office. Some people can also apply online at www.socialsecurity.gov/applyforbenefits. It is important to complete the form with as much information as possible. Give the full names and addresses of all doctors, and the dates of any hospitalizations. Make a list of the medications or other treatments used, their side effects, and any medications and treatments which have been tried but which no longer work. Describe the child's daily activities, and mention whether his/her behavior or weight prevent him from performing certain activities. Tell the child's doctors that he/she is applying for disability benefits, and that the doctor should expect to receive a request for more information from SSA. Many claimants wait until a hearing is scheduled before hiring an attorney to represent them, but you can choose to be represented at any stage of the application process.

Application and Appeals Process

Only about 30% of disability applications will be approved at the first step of the process. If your application is initially denied, there are several steps in the appeal process.

When your claim is denied initially, you should appeal by completing a reconsideration form. You have 60 days to request reconsideration. A different person from SSA will evaluate your claim. You may have to wait a year before you receive a decision at this stage.

You should be aware that SSA is experimenting with eliminating the reconsideration step. Therefore, in some parts of the country, instead of requiring reconsideration of a denial, you would request a hearing before an ALJ. In most areas, you do not request a hearing unless your claim has been denied at the reconsideration level. Your local SSA office or your representative will know which type of appeal you should file.

If you are denied at the reconsideration level, you will have 60 days to appeal to an Administrative Law Judge for a hearing. Over half of the claimants who request a hearing before an ALJ will receive favorable decisions awarding benefits. At the hearing the ALJ will ask you about your child's condition and how it affects your child's ability to work and perform activities of daily living. The ALJ will ask what your child can do during the day and how the child feels after doing certain activities. Family members may also tell the ALJ about your child's condition. The ALJ may also ask a medical expert to explain Prader-Willi syndrome. You can help your claim by providing information to the ALJ before the hearing. The ALJ may also call a vocational expert who will talk about what jobs your child could perform and whether a significant number of these jobs exist. If your child has worked in the past, the ALJ will also ask the vocational expert whether your child can perform the work that he/she did before.

If the ALJ denies your claim, you have 60 days to appeal to the Appeals Council. In some parts of the country, SSA has eliminated the Appeals Council, so you would appeal directly to federal court. An Appeals Council appeal is a written form. If you disagree with the ALJ's decision, you or your representative must explain exactly what parts of the decision you think are wrong. Occasionally, the Appeals Council will ask your representative for oral argument. But this is very rare. Unfortunately, it is not uncommon to wait 1-1/2 years before the Appeals Council makes a decision. The Appeals Council will usually either send the claim back to the ALJ for another hearing or deny your claim altogether. Eighteen percent of the claims are sent back for another hearing. The Appeals Council finds that claimants are disabled without another hearing in only 2% of the appeals.

If the Appeals Council denies your claim, you can appeal to federal court. You have 60 days to file a claim in federal court. You will want representation at this level, as only an attorney can file an appeal in federal court; a non-attorney representative cannot appeal to federal court.

How Long Will the Application Process Take?

It is not uncommon for a claimant to wait 6 to 12 months for a decision on an application for disability benefits. Claims that must be appealed administratively (to an Administrative Law Judge and the Appeals Council) or to federal court will take much longer. (To provide some perspective on the program, consider that almost 3 million applications for disability benefits were filed in a recent year.) When a case is finally approved, benefits will be paid to cover the months during which the

claimant was waiting for a decision. The amount of time and effort it takes to pursue an appeal is definitely daunting. Perseverance and persistence are crucially important.

What Determines the Benefit Amount?

The amount of Social Security Disability Insurance, or Title II, benefits paid depends on the former worker's earnings throughout his/her work history, the number of years worked, his/her age, as well as the number of people in the family and its composition (including divorced spouses). For a person whose earnings, averaged over his/her working life, were $20,000, Title II disability benefits in 2005 would be approximately $835 monthly. A spouse and child would receive an additional $415. For a person whose earnings averaged $50,000, the monthly benefit amount could be approximately $1,570. The family maximum, a cap on the monthly benefits payable on the account of a particular worker, limits the amount of Social Security benefits payable to an entire family when all benefits are based on the account of one wage earner. The effect of the family maximum, however, is that families with more children may not necessarily receive more benefits than families with fewer children, even if the Personal Income Account figures are the same.

Note that there is no family maximum for SSI benefits because each person who receives benefits does so based on his/her own impairment. It is possible, then, that a very poor family with several disabled children will receive more SSI benefits than a wage earner and dependents receiving SSDI (Title II) benefits.

The SSI benefit amount is based on the income, resources, and living arrangement of the disabled individual, and sometimes, his family. There is a federal SSI monthly benefit rate: in 2005, $579 for an individual and $869 for an eligible couple. Many states add a state supplement to this amount. An individual's monthly SSI benefit will be reduced by other resources and income he receives, based on SSA's formula for counting "earned" and "unearned" income. The amount of the SSI check can differ each month if the amount of income changes each month. The formula can be quite complicated. Although SSA is required to provide an explanation of how the benefits amount is calculated, it is still recommended that you ask your representative to explain the decisions in your specific case.

SSA uses a "Retrospective Monthly Accounting" method. This means that the amount of SSI benefits in any given month is determined by the income received in the second previous month. For example, the November SSI amount is based on income received in September.

In certain situations, SSA will count a portion of *another person's income* as the unearned income of an SSI recipient. This is called "deeming." It does not matter whether the other person's income is actually available to the SSI recipient. For example, if one spouse is disabled and not working, the income of the other spouse will be deemed to the disabled spouse and will affect his/her eligibility

for SSI benefits. A parent's income is deemed to a minor child and will affect the child's eligibility for SSI and benefit amount, if found eligible. This is why the disabled child in a middle class working family will not be eligible for SSI benefits. The income of a parent's spouse will also be deemed to the child, even if the spouse has not adopted the child. Deeming does not always apply if the child does not live with the parent. Special deeming rules exist if the child lives in a Medicaid-funded institution, or lives with another relative. Parent-to-child deeming ends when the child turns 18 years old. Even without deeming, this does not mean a child will be eligible for SSI. SSA looks at living arrangements also. In some states, a child who is not financially eligible for SSI may still be eligible for Medicaid. Certain types of income, such as other types of welfare benefits, are not deemed.

When determining the monthly SSI benefit amount, SSA will also consider the individual's living arrangements. If an SSI recipient lives with another person and receives food, clothing, or shelter from that person, SSA calls this "in-kind support and maintenance" and includes the value as income. If the SSI recipient can show that he has been *loaned* the support and maintenance and has an obligation to repay it, it will not affect the amount of assistance.

If an SSI recipient is living in another person's house and receiving both food and shelter from that person, SSA will apply what is called a "one-third reduction rule." However, if the recipient is paying a pro rata share of household expenses, or buying his own food, then he is not considered to be living in the household of another and is not subject to the one-third reduction rule. Instead, he is subject to the "presumed value rule."

The main difference between the one-third reduction rule and the presumed value rule is that, under the one-third reduction rule, SSA will reduce the federal monthly SSI benefit by one third ($193, based on the 2005 monthly benefit of $579). The actual value of the support does not matter. Under the presumed value rule, SSA starts with a presumption that the value of the in-kind support is worth one third of the federal benefit rate. However, if you can show that the actual value is less than one third of the federal benefit rate, SSA will use the lower number and will reduce the SSI check by the lower amount.

In addition, SSA will deduct other income, as well as disregard certain amounts of earnings before determining the monthly benefit amount.

Once Approved, Can I Work and Continue to Receive Social Security or SSI Benefits?

SSA has many work incentive programs, which allow recipients to work for a limited amount of time, or under special circumstances, without losing their benefits. Most people who receive Social Security Disability benefits can earn up to $590 per month (in 2005) for 9 months

while receiving their benefits. This is called a Trial Work Period. After the 9 months are completed, a beneficiary can work during the following 3 years. Benefits will not be paid for any month in which you earn over $590, but you will receive benefits for any month you do not work. If you are still working at the end of the 3-year period, benefits may be terminated.

Another work incentive available is called Impairment Related Work Expenses (IRWE). If you have certain expenses because of your disability that permit you to work, you can deduct the cost of these expenses from your income. For example, if your seizures prevent you from driving, and there is no public transportation available, or if you are unable to take public transportation, the cost of a taxi to and from work can be deducted from your earnings. SSA will deduct the difference between the cost of the taxi and the cost of the bus that you cannot use. Deducted expenses will not be counted as earnings. This can be used to bring your earnings below the monthly Substantial Gainful Activity level ($830 for 2005). The amount of money considered an IRWE will not be counted as income and will not cause a reduction in your SSI check.

You can also create a PASS Plan. This is a Plan for Achieving Self Support. A PASS plan is a written plan that must be approved by SSA in advance. It permits you to set aside some money earned towards an educational or occupational goal. The money set aside will not be counted as income for Title II or SSI purposes. This can be used to bring your earnings below the monthly substantial gainful activity level, and SSA will then find that you are not "working." The amount of money set aside under a PASS plan will not be counted as income and will not cause a reduction in your SSI check.

SSA has recently started a "Ticket to Work Program," which also permits recipients of disability benefits do to some work while receiving benefits and continued Medicare coverage. People can use their Ticket to get free vocational rehabilitation, job training, and other employment support services. SSA's Web page has information on the Ticket to Work Program and other work incentives that are available. Look at www.socialsecurity.gov or call SSA at 1-800-772-1213.

It is not advisable to return to work before you have received a favorable decision on disability applications. Recipients who are considering trying to work should look at SSA's Web page, and contact SSA at 1-800-772-1213 or an attorney who is familiar with Social Security programs for specific guidance.

How Can I Get Help or Additional Information?

Additional information can be obtained from SSA by calling 1-800-772-1213 or looking at their Web page at www.socialsecurity.gov. Most people apply for benefits on their own but often want assistance in pursuing an appeal. If you need legal representation to assist you in obtaining Social Security disability or SSI benefits, contact your local

legal services program or your local bar association referral office. Or you can get a referral to a private attorney in your area from the National Organization of Social Security Claimants' Representatives by calling 1-800-431-2804.

Appendix E

The International Prader-Willi Syndrome Organization

The International Prader-Willi Syndrome Organization (IPWSO) is a global organization of 60 member and associate countries committed to enhancing the quality of life for people with Prader-Willi syndrome and their families, giving our children the best possible opportunities for living their lives to the fullest. This international community of parents, friends, and professionals forms a dedicated network. It connects families and professionals, provides emotional and educational support, spreads general awareness, educates, and encourages scientific research. Regional and international conferences are especially helpful in giving families the occasion to come together for educational workshops and lectures, while also providing a forum for scientists.

Most significantly, IPWSO helps families—even in the most remote corners of the world—understand that they are not alone in dealing with the challenges of this complex syndrome. We provide a window to support and services that already exist within a member country. Where no support exists, we help fledgling associations with their development.

Since education promotes the possibility for early diagnosis and early interventions in medical and behavioral management, spreading awareness is a major goal of IPWSO. Our educational packets ("General Awareness," "Crisis," and "Medical Awareness") cover a wide range of essential topics and are distributed throughout the world in many languages.

IPWSO is an organization without borders—open to people of all origins and cultures. Families, researchers, clinical physicians, and other professionals from all over the world are a part of our network and our family. Please check our Web site (www.ipwso.org) to see if your country has a national association. If it doesn't, contact us and we will assist you in forming an association, and we will connect you to other resources in your region, as well as throughout the world. We invite you to join our global family. With nations working together and sharing our resources and goals, IPWSO provides a beacon of hope for a better life for children with PWS and their families. With love and determination, all people with PWS can have a brighter future!

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The Prader-Willi Syndrome Association (USA)—PWSA (USA)—is the only national membership organization for children and adults with Prader-Willi syndrome and their families in the United States. PWSA (USA) has been serving children and adults with the syndrome for nearly 30 years. At the time of this writing, the Association also has 33 state and regional chapters, which carry out a range of activities to serve local families and support the mission of the national organization. PWSA (USA) became incorporated in 1977 and was approved for tax-exempt 501(c)3 status as a charitable organization by the U.S. Internal Revenue Service. By 1988, the Association had become a multifaceted international organization, and it currently serves members from 32 other nations in addition to its U.S. members.

Educational Materials—No other resource in the world provides as extensive a range of educational and syndrome management publications as those provided by PWSA (USA). Thanks to thousands of hours of donated time and skills by professionals and parents (often parents who are professionals in a related field), PWSA (USA) provides 35 educational books and/or booklets, 14 brochures, and several videos that cover various topics on medical, emotional, and behavioral management. PWSA (USA) mails, at no cost to the recipients, thousands of awareness and educational packets yearly. Association members are regularly kept up to date through PWSA's bimonthly newsletter, *The Gathered View*, and through articles posted on the PWSA (USA) Web site.

National Conference—The annual national conferences sponsored by PWSA and hosted by the state chapters are the largest in the world (averaging over 1,000 attendees) specifically for education and support for those dealing with Prader-Willi syndrome. This conference is actually several conferences occurring simultaneously—for scientists and other medical professionals, for adult service providers and teachers, for parents and relatives, for those with PWS, and for siblings.

Research—PWSA (USA) has two active medical advisory boards. Its Scientific and Clinical Advisory Boards are comprised of volunteer professionals from around the nation who are researchers and/or medical specialists who treat individuals with the syndrome. PWSA (USA) grants small start-up funding for research projects. The Association also impacts research in many other ways such as advocating for government and private funding of research projects, networking researchers, and through its Clearinghouse Project for research data on PWS.

Medical Intervention Support—Hospitals, physicians, and parents from all over the world consult with PWSA (USA) for medical emergencies and questions daily. Through phone, fax, and e-mail, PWSA (USA) consults with its medical boards and responds to all through a Triage Support System.

Crisis Intervention and Prevention Program—A significant role of the national office is to assist with crisis situations. This is done through the support of a qualified crisis counselor via phone and e-mail consults and networking with specialists on the syndrome from around the nation, PWSA publications, and individualized crisis packets, each containing very specialized letters to address the crisis at hand (see Chapter 19). Our executive director, the crisis counselor, and several of the medical board members consult with attorneys and teleconference with schools and courts.

New Parent Mentoring Program—Coordinated and supported by parent volunteers, this program has the greatest impact on early intervention and prevention, as experienced parents work one-on-one with newly diagnosed families. Early diagnosis, education, and awareness are the keys to prevention of life-threatening obesity and years of isolation and emotional trauma to the family of the child with Prader-Willi syndrome. Early intervention can also save thousands of dollars in medical expense and greatly reduce emotional stress on families.

Bereavement Follow-up Program—This program consists of four separate mailings to bereaved families within the first year after the death of their child. This support program also includes a one-time packet to PWS parents who lose a spouse or another child. Bereavement phone support is also offered.

Technology and International Support—Traffic to PWSA's Web site averages over 38,300 visits a month. Thanks to e-mail, PWSA (USA) has also been able to more effectively support families in the United States and provide support for those in many other nations who have no support system. As stated in a recent e-mail from Giorgio Fornasier, a parent from Italy who is the immediate past president of the International Prader-Willi Syndrome Organization (IPWSO), with which

PWSA (USA) is affiliated: "Technology is also a 'means,' not something to show we're different, inferior, or superior. E-mail is a fantastic way to communicate and assist people, and the Internet a window in the world which any desperate family can open and realize the sun is shining."

The Executive Director of PWSA (USA), Janalee Heinemann, states: "Our short-term goals are to support and educate parents and professionals and to save the lives of our children in crisis. Our long-term goal is to continue to enact our mission statement with a particular emphasis on *preventing* our children from getting into a crisis state. Our mission is not only to educate the families and professionals working with the syndrome, and to save the lives of our children, but also to foster the emotional well-being of our children and young adults with PWS. To give them a sense of worth in a society that shuns anyone different and views obesity as a psychological weakness is not an easy task. Today, understanding, acceptance, and wholeness are only in the dreams and wishes of our children and their families—but our ultimate goal."

PWSA (USA) Educational Materials

Following is a selected list of educational products available through PWSA (USA) as of April 2005:

Publications in English

The Child With Prader-Willi Syndrome: Birth to Three, by Robert H. Wharton, M.D., Karen Levine, Ph.D., Maria Fragala, P.T., Deirdre C. Mulcahy, M.S., CCC–SLP. This booklet discusses the common concerns of the first 3 years and offers specific recommendations for early intervention strategies. A helpful and positive resource for families, physicians, early intervention worker, and other care providers. 34 pages (revised 2004).

Prader-Willi Syndrome: Handbook for Parents, by Shirley Neason, with subsequent revisions by members of the PWSA publications committee. A comprehensive booklet with pictures that covers birth to adulthood. Parent-to-parent handbook for understanding and managing issues related to PWS. 75 pages (revised 1999).

Nutrition Care for Children with PWS, Infants and Toddlers, by Janice Hovasi Cox, M.S., R.D., and Denise Doorlag, OTR. Provides answers to frequently asked questions about nutrition and feeding of infants and toddlers with Prader-Willi syndrome. 62 pages (revised 2004).

Nutrition Care for Children with PWS, Ages 3-9, by Karen H. Borgie, M.A., R.D. Covers calorie needs, supplements, diet planning and food management, and explains food exchange lists. 12 pages (2003).

Nutrition Care for Adolescents and Adults with PWS, by Karen H. Borgie, M.A., R.D. Covers essential diet information for families, caregivers, and residential service providers. 24 pages (2003).

Low-fat, Low-sugar Recipes for the Prader-Willi Syndrome Diet, by Donna Unterberger. Cookbook for the PWS diet filled with recipes designed

for use by the whole family. Great substitution list, fun snack recipes, mealtime tips, and full nutritional values calculated for each recipe. 156 pages (2003).

Physical Therapy Intervention for Individuals with PWS, by Maria Fragala, P.T. This booklet provides general information about physical therapy intervention. Includes copies of articles by Janice Agarwal, a physical therapist and mother of a young child with PWS. 11 pages.

Exercise and Crafts & Activities—A Collection of Articles. Contributions by Jennifer C. Deau, M.S., exercise physiologist, and other articles on muscle tone, upper body strength, exercise, and crafts and activities for the individual with Prader-Willi syndrome from infancy to adulthood. 44 pages (1998).

Behavior Management—A Collection of Articles. This booklet includes articles on behavior management and specific concerns, such as use of psychotropic medications, management of skin picking, toilet training, social skills teaching, and more from PWSA's newsletter, *The Gathered View*, and other sources. 79 pages (revised 2003).

Educator's Resource Packet, including the booklet *Information for School Staff: Children with Prader-Willi Syndrome*, by Barbara Dorn, R.N., and Barbara J. Goff, Ph.D. This packet is a resource for educators that includes a teacher's handbook for the student with PWS, an accompanying worksheet about PWS-related issues and interventions for school staff, as well as related articles from PWSA's *The Gathered View*. (2003).

Health and Medical Issues for the Individual with Prader-Willi Syndrome—A Collection of Articles. From the pages of PWSA's newsletter, *The Gathered View,* and other sources, this booklet brings together articles on many aspects of PWS written primarily for the layperson. Covers management of obesity, various medical conditions associated with the syndrome, vision and dental issues, sexual development and sexuality, genetics of PWS, and more. 121 pages (revised 2004).

Prader-Willi Syndrome Medical Alerts. Important resource for parents to give to their child's doctor, emergency room staff, caregiver, etc. Briefly presents cautions regarding aspects of PWS that could lead or contribute to life-threatening situations. A useful pocket-sized handbook written by PWSA's medical professionals. 20 pages (2005).

Growth Hormone and Prader-Willi Syndrome—A reference for families and care providers, by Linda Keder in consultation with both medical and parent advisors. Covers growth patterns in PWS, research on the effects of growth hormone treatment, and details on using GH therapy in children with PWS. 52 pages (2001).

Prader Willi Syndrome Is What I Have, Not Who I Am! A book of "feelings" written by children and young adults with PWS, collected by Janalee Heinemann, Executive Director of PWSA (USA). This book gives insights into the lives and thoughts of people dealing with PWS on a daily basis. A portion of the book opens the door to journal writing and an opportunity for the reader with PWS to share their feelings. (2005).

Michael and Marie, Children with Prader-Willi Syndrome, by Valerie Rush Sexton and Debbie Erbe Fortin, illustrated by Bonnie Branson.

Written by two teachers, this storybook is designed to be read to elementary school age children to educate classmates of special needs children about the need to understand and help create a friendly and safe environment for all children. (2003).

Sometimes I'm Mad, Sometimes I'm Glad—A Sibling Booklet, written by Janalee Heinemann, M.S.W., in the voice of a sibling of someone with PWS. Recognizes the range of feelings that arise in having a brother or sister with the syndrome, based on the author's observations in raising her son with PWS and his siblings. (1982).

Supportive Living Care Plan for an Adult with PWS in Placement. This comprehensive book/CD will help families create a plan that is specifically designed to help staff and supportive personnel provide predictable, consistent, and accountable care and advocacy for the adult with PWS. This is available in both a notebook format and in a changeable CD that can be adapted to explicitly meet the needs of each individual. (2002).

Video Products

"PWS—The Early Years" (42 minutes). This video offers help and practical suggestions for those families with a young child newly diagnosed with PWS. Genetics, medical, early intervention, and family issues are presented, personalized with family interviews. Although focusing on young children, this video is a wonderful resource for schools and families with children of all ages. PAL European version available. (2002).

"Prader-Willi Syndrome-An Overview for Health Professionals" (35 minutes). This outstanding medical overview video is a must for all health care professionals who are not "experts" on Prader-Willi syndrome. It deals with all the major genetics and health care issues of the child with PWS. PAL European version available. (2002). New DVD version available (revised 2004).

"Understanding Prader-Willi Syndrome" (18 minutes). A professionally produced video with good practical advice for individuals who work with persons who have PWS, designed to train service provider staff on the needs of individuals with PWS.

Publications in Spanish/Literatura en Español

Mi Hija tiene el síndrome de Prader-WillidY ahora qué? by Carlos Molinet Sepulveda. The experience from a Chilean father's perspective of searching for answers about his daughter, who was born in 1988 with Prader-Willi syndrome in a country with no knowledge or resources on PWS. He tells a moving story about the power of love and perseverance. (2003).

Guia Para Familias y Professionales El Syndrome de Prader-Willi. Comprehensive book on the management of PWS, each chapter written by a specialist on the particular topic. Excellent reference tool. Reprinted thanks to Asociacion Espanola Prader-Willi. Softcover, 400 pages. Also available in CD format.

Sindrome de Prader-Willi: Guia Para Los Padres, Familiares Y Profesionales, by Moris Angulo, M.D. An overview of the syndrome in booklet form for parents and professionals. 16 pages (revised 2003).

Note: This is not a comprehensive list of PWSA's publications and videos, and available titles may change over time. For a current order form that includes all available products contact the PWSA (USA) office or visit the Association's Web site: www.pwsausa.org.

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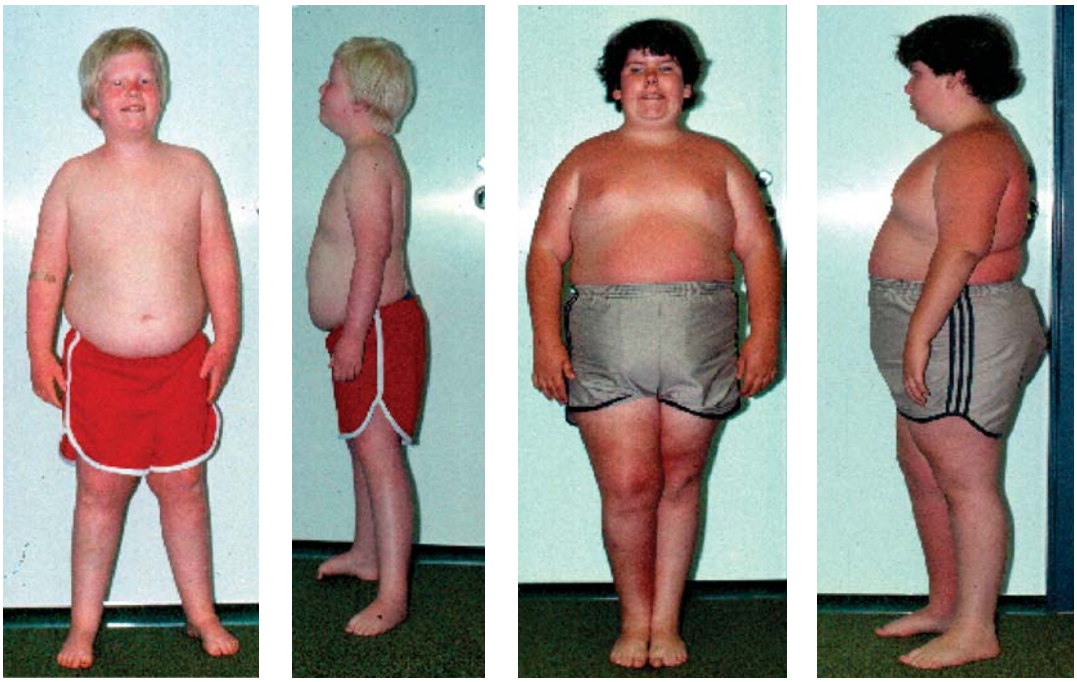

A B

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.[17]

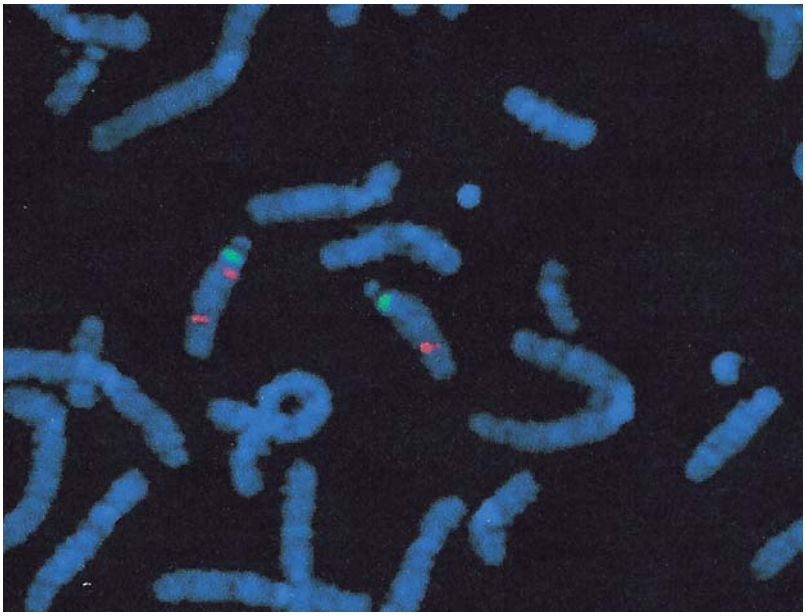

Figure 1.4. Representative fluorescence *in situ* hybridization (FISH) using a SNRPN probe from the chromosome 15q11-q13 region (red color), a centromeric probe from chromosome 15 (green color), and a distal control probe from chromosome 15q (red color) showing the absence of the SNPRN signal close to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

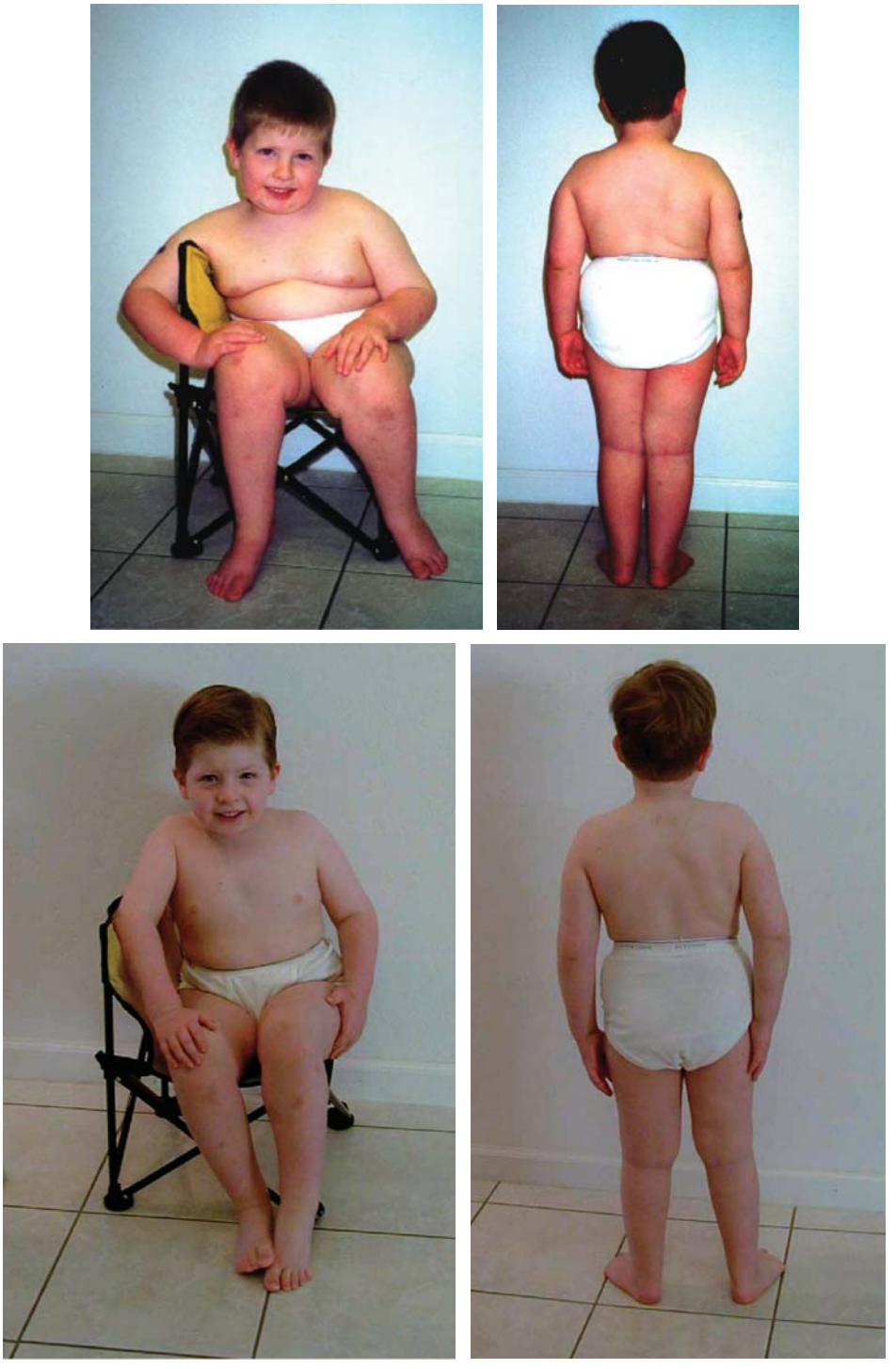

Figure 1.5. Five-year-old boy with Prader-Willi syndrome before (top) and after 3 months of growth hormone (GH) treatment (bottom). Note the improved body habitus, muscle bulk, and reduced fat. The patient was able to increase total caloric intake, and he had increased activity and wakefulness. Reprinted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