Regulation of Weight in Prader-Willi Syndrome: Theoretical and Practical Considerations

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Introduction

These questions have been raised by nearly everyone who comes in contact with a persons with Prader-Willi syndrome: What is the defect in weight regulation that sets PWS apart from typical obesity? How is the problem to be managed? Does every person with the syndrome require the same approach?

The answers are complex and require more than short term observations of persons with PWS. Observers who have had long term experience with the syndrome have come to understand the following;

- The defect is severe and life threatening;
- Short term behavior with respect to food does not predict long term weight regulation capability;
- Behavior with respect to food is highly dependent on an individual's *past* experience and *current* opportunity.

Theoretical Considerations

We do not yet know the precise defect(s) leading to weight dysregulation in PWS. However, by examining how weight is regulated in typical persons and in animals, we may better appreciate the situation with PWS.

There are 3 categories of factors that potentially control body weight over time:

- **Self-regulation**
- **Environment**
- **Physiology**

The least potent of these categories is self-regulation (the voluntary calorie restriction and deliberate calorie expenditure); it has a minimal role in control of body weight (Peters et al. 2002). Self-regulation has no role in the weight maintenance of birds and animals. The body weight of many profoundly retarded or senile persons is remarkably consistent over time. The point is that *weight regulation is not a voluntary choice involving cognitive (cortical) processes.*

In the Framingham Study the body weight of the average adult increased by only 10 percent (less than a pound a year) over a 20-year period (Belanger 1988). These data were collected before the worldwide obesity epidemic that appears to have begun in the 1980s and accelerated in the 1990's.

The current worldwide epidemic of overweight and obesity (figure 1) is generally attributed to a change in the **environment** (Hill et al. 2003; WHO 2000). Never before in human history has food been so inexpensive, convenient and tasty. Statistics reveal that most persons (greater than two thirds of us) gain excessive weight over time when environmental constraints on the food supply are no longer operative, and physical activity is optional rather than

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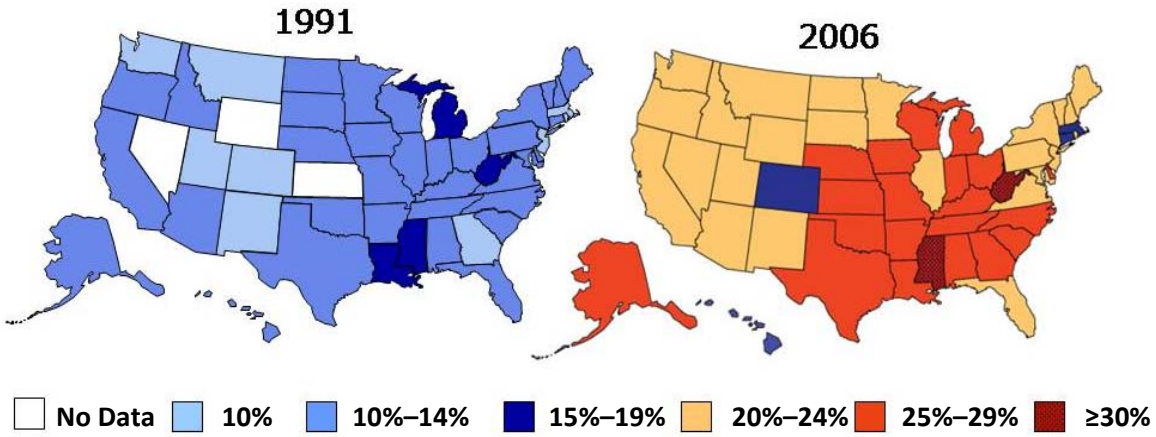


Figure 1 Obesity Trends in US Adults 1991-2006
The proportion of adults who are obese (BMI of 30 or more) has more than doubled in the last 15 years. Childhood obesity has tripled in prevalence. Two thirds of US adults are currently overweight or obese and this proportion is increasing yearly. No one has devised a proven method for slowing this epidemic trend among typical persons whose physiologic tendency to gain weight is miniscule compared to that found in PWS.

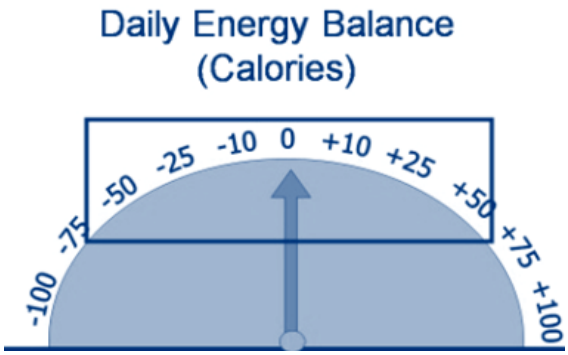
necessary for our survival. Research on general obesity is painting a dismal picture about our ability to learn to regulate our body weight under these environmental conditions, battling an inherited, ***physiologic*** tendency to conserve energy and to gain weight.

PWS and the Rest of Us: Orders of Magnitude

What separates the slow steady weight gain of the typical overweight person from the rapid weight gain possible in PWS is **physiology.** *It is easy to underestimate the physiologic defect in PWS with respect to body weight regulation.* Typical persons who are morbidly obese are thought to be taking in less than 100 excess calories (kcal.) per day Figure 2), or less than 2-5% excess over their daily energy usage. The net effect is an annual weight gain of *well under* 10 pounds per year. This appears to be what typically occurs in susceptible persons.

Other persons, those of fortunate genetic makeup maintain a perfect daily energy balance and a healthy weight year after year. This weight regulation is a *not* a voluntary process. A number of complex neurohumoral (neural and hormonal) signaling systems are involved in slowing or preventing weight gain. These include messages to the brain that make further consumption of calories unappealing, nauseating or even painful. **These signals have been shown to be delayed, weak, and short lived in persons with PWS allowing them to consume comfortably *6 times* their actual calorie needs and, in**

Figure 2 **Normal physiology allows us to regulate our daily energy balance within a very narrow range of variation. The hypothalamus tightly regulates our intake and our usage of energy without any conscious effort on our part; it responds automatically to signals from the body's fat mass, the intestinal tract and lean body mass. Typical overweight persons add weight very slowly as a result of a relatively small imbalance in their daily energy.**



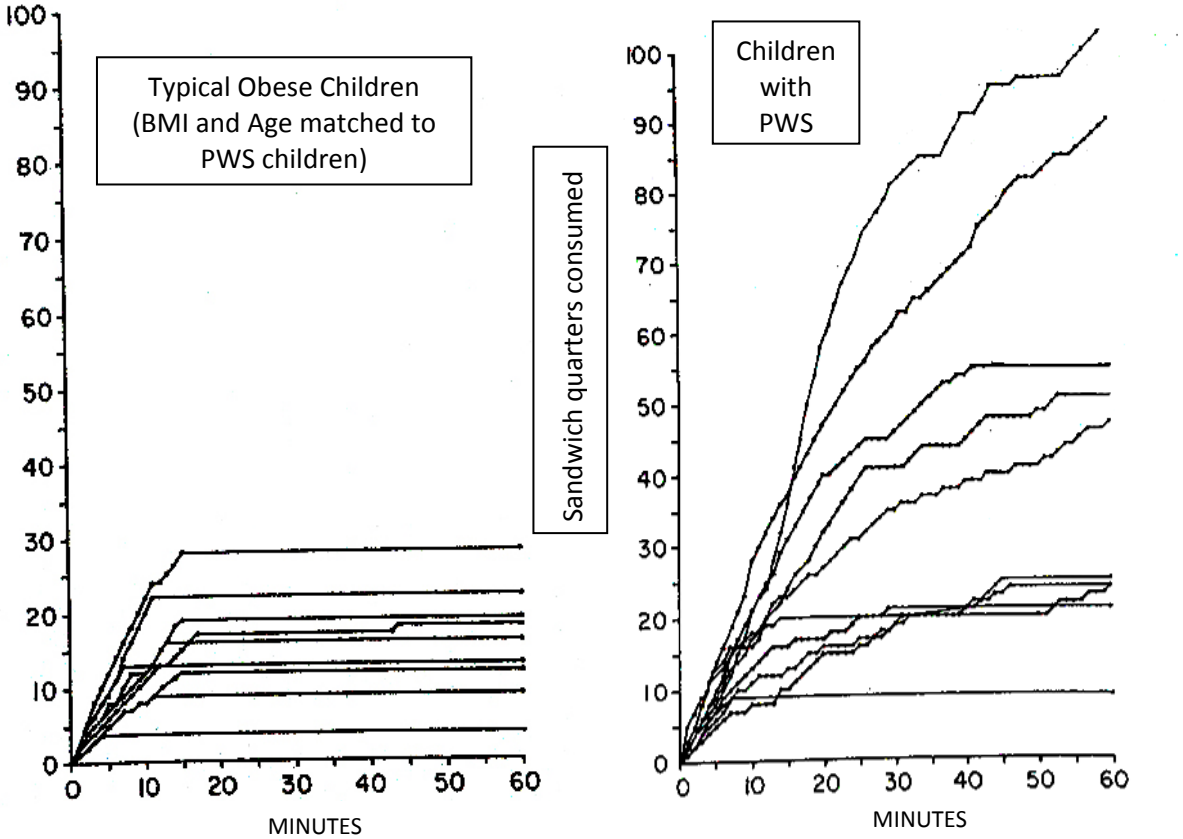


Figure 3 In this study children with PWS were compared to typical obese children matched for age and BMI. They were permitted to consume sandwich quarters freely for 1 hour. The children with PWS consumed on average 3 times as many calories as the typical children which was roughly 6 times their actual calorie needs! Other studies have shown similar results. (Zipf & Bentson *Am J Clin Nutr 46:277-281, 1987*)

documented cases, far more. (Figure 3) Further, typical overweight persons have two mechanisms available to slow their weight gain: they expend more calories than lean individuals due to an increased body mass *and* in muscle mass; and their metabolism becomes less efficient, thus wasting calories (Leibel et al. 1995). Neither mechanism is available to persons with PWS. Their muscle mass is smaller than normal, and their hypothalamus is less responsive and likely does not recognize and adjust their metabolism when they are gaining weight. Typical overweight persons who have lost weight appear to have a physiologic challenge similar to people with PWS. After a typical person loses weight, satiety signals are reduced (Cummings 2002) and muscle efficiency is increased. Thus the number of calories used by exercise is reduced by about 15% (Rosenbaum et al. 2003). As a result, *the vast majority of highly motivated persons* (95%) who are capable of significant weight loss through self-regulation regain their lost weight over time. Those who are (relatively) successful depend heavily on large amounts of calorie expenditure through an average of one hour of exercise per day (Hill et al. 2005). Due to their smaller muscle mass, persons with PWS are much more limited in their ability to increase their calorie expenditure through exercise; they have no hope of achieving an energy balance by that means alone. Even with exercise, they will gain weight eating a normal diet.

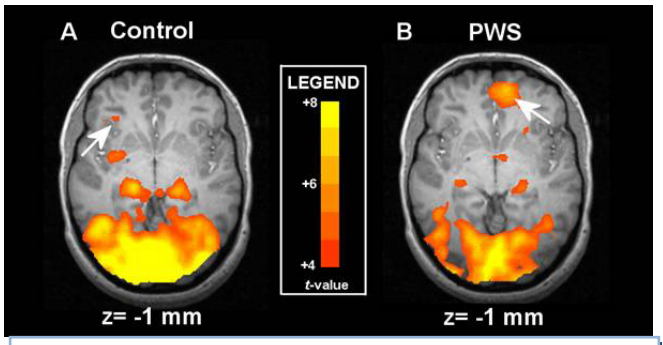


Figure 4 Increased activation when viewing food pictures immediately after 500 kCal meal in: OFC, insula, parahippocampal gyrus, medial PFC, amygdala.
Miller et al. 2007 (Used with permission)

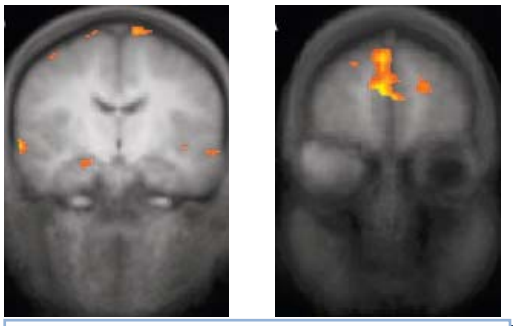


Figure 5 Increased medial PFC activation when viewing food pictures 10-25 mins after oral glucose
Holsen et al. 2006 (Used with permission)

Some clinical observations of responses of persons with PWS to food and fasting have been intriguing. *Persons with PWS appear to enjoy food more.* Further, they may find foods or even inedible items that are unpleasant for others to be enjoyable. We have anecdotes of persons eating raw meat, spoiled food, and pet or fish food and reporting these items to be satisfactory to their taste. Some clinicians have interpreted this willingness to eat distasteful items as evidence of their "ravenous hunger". But there is a different interpretation. Rather than assuming extreme hunger at the beginning of a meal, there is reason to believe that the defect involves the failure to respond normally at the end of a meal. The defect appears to be in the sense of satisfaction or fullness (called satiety) that normally comes with eating. Both behavioral observation studies (see Table 1 on page 10) and more recent brain imaging studies have demonstrated abnormalities in the response of persons with PWS following the ingestion of food.

Functional MRI (magnetic resonance imaging) studies and PET scans (positron emission tomography) can look at areas of brain activation during mental activities under specific conditions. In a 2005 study, Shapira et al. reported that brain activity in satiety centers was delayed by 24 minutes after administration of glucose to subjects with PWS. Healthy lean subjects showed delays of 10 minutes, and obese subjects showed delays of 15 minutes.

Hinton et al. (2006) also demonstrated that PWS persons displayed markedly abnormal brain activation in response to a meal. The areas that failed to activate were those that activate in typical persons after eating. Further, the data was interpreted to suggest that some of the subjects felt more satisfied in the fasting state than after a small meal. This finding echoes the observations of some families and clinicians that eating behavior *enhances* interest in food for persons with PWS. This study also confirmed prior observations that feelings of fullness returned to the fasting level 2 hours following a high calorie meal.

The brain activity of typical and PWS persons has been localized and quantified while they viewed food pictures during the fasting state and following a meal. Holsen et al. (2006) found that study subjects with PWS not only responded to food stimuli *more* than healthy weight controls, but also the magnitude of response was greater *after* a meal than before the meal. Miller et al. (2007) studied functional MRI images of the brains of persons with PWS while they viewed pictures of food after what should have been a satiating (satisfying) ingestion of glucose. Their results suggested that enhanced reward contributes to the hyperphagia (overeating) of PWS. Dimitropoulos and Schultz (2008) demonstrated more activation in brain reward centers in response to high calorie foods than to lower calorie foods.

There are paradoxical clinical observations as well. Families have reported that *their child with PWS can be relatively indifferent to fasting as long as they are assured of the arrival of the next opportunity to eat.* Prolonged fasting as a result of a medical condition has also been noted to result in less, not more, interest in food. And, of course, as every parent knows, young infants with PWS universally appear to be indifferent to hunger and to eating.

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Discussion

Neural and humoral (nerve and hormone) signals control both short term energy intake/use as well as long term body weight regulation; they provide tonic continuous feedback to *prevent or slow* weight gain. Persons with PWS appear to have abnormalities in both short term and long term regulatory functions. An imbalance of short term energy intake allows excessive calorie intake meal by meal, day by day. **Leptin**, a messenger produced by fat tissue, is present in normal levels in PWS, but it fails to deliver the message that for the rest of us stabilizes weight over time. The brain's apparent insensitivity to this messenger even at high levels allows persons with PWS to rapidly accumulate a large amount of adipose tissue (fat). **Ghrelin**, the "hunger hormone", is often elevated in persons with PWS but there is reason to believe that the brain is relatively insensitive to this messenger, as well. It is not at all clear that ghrelin is driving the excessive intake. The difference between persons with PWS and other weight gaining persons may only be a matter of degree, but the degree of abnormality is extreme (Figure 6). For the rest of us, satiety (sense of fullness) signaling is a powerful force that begins within seconds of commencing a meal; after 10-15 minutes of eating even the most delicious food, we can say, "I couldn't eat another bite!" What has given us great pleasure minutes before has become unattractive, even repulsive. These powerful "brakes" are not functioning well in PWS.

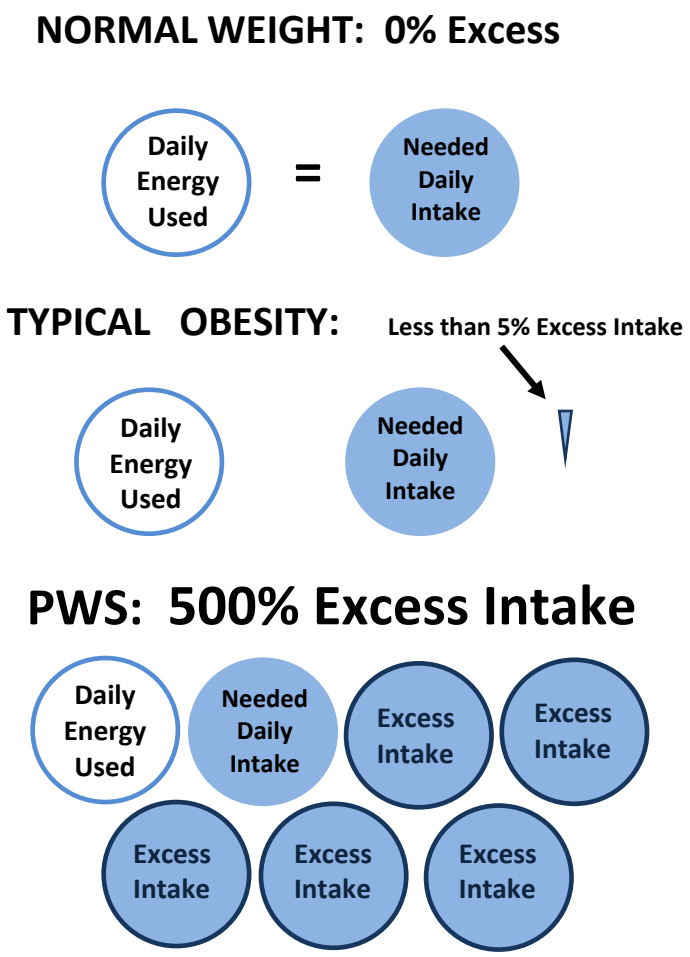

Figure 1 **Daily Energy Imbalance**

Typical overweight or obesity is the result of a relatively small error in average daily energy balance. For example, a 5% excess of intake over expenditure, if maintained, allows a person to gain on the order of 5-10 pounds per year. If this is allowed to continue the typical person therefore will take 10 or more years to become morbidly obese (roughly 100 pounds overweight).

By contrast, in the sandwich study, children with PWS were observed to ingest (on average) 6 times (or 600%) their daily energy needs, an error of **500%!** This explains why moderate interventions can slow, but ultimately fail to stop, the relentless weight gain associated with the syndrome. Caretakers of some adults with PWS have repeatedly documented 20-30 pounds of weight gain in a matter of days when free access to food was possible.

The calorie imbalance defect in PWS is on the order of <u>100 times</u> that suffered by ordinary overeaters!!

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The results of neuroscience research have helped us to better understand the relationship between hunger and satiety. Each is the result of positive signals; one is not merely the absence of the other (see model below). The neurohumoral relationships are exceedingly complex as are the defects present in PWS and both are incompletely understood. However, direct clinical and research observations, together with reports from caretakers and families, suggest that both hunger and satiety signals are blunted or diminished in PWS (along with other types of feedback such as feelings of disgust and pain). The neuro-imaging studies, while very preliminary, appear to be pointing to a similar conclusion. What drives the excessive food intake may not be hunger so much as the ***reward*** of eating. Neuroscientists have studied the reward circuitry in the brain extensively, and it is known to be a very powerful influence on our behavior. It can be hypothesized that infants with PWS have little motivation to eat due to minimal hunger and the extra effort (due to the hypotonia) required to eat or complain (crying); they will require experience to teach them of the pleasures of eating and will experience, with time, an ***enhanced*** **reward** associated with food. Many observers have commented that persons with PWS appear to derive intense enjoyment from their mealtime experience. This enhanced reward associated with eating may be the result of the delayed and diminished satiety signals that would normally balance the reward of eating. Sometimes families and caregivers offer highly pleasurable foods to persons with PWS to compensate for the small amounts of food they are permitted to eat. But it may be that small servings of rich and sweet foods leave them more unsatisfied than less enticing fare!

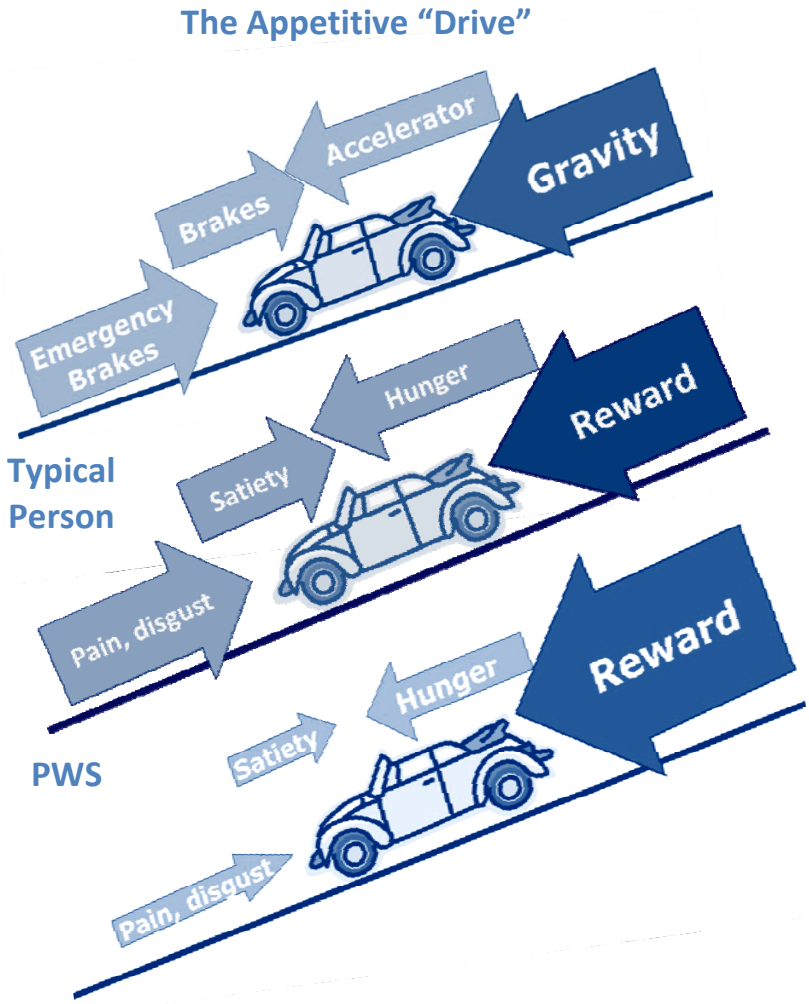

Figure 7

The Appetitive "Drive"

A Schematic of Vectors Modulating Energy Intake

This analogy compares a car on a hill to a typical person and to a person with PWS in a food rich environment and illustrates the multiple forces acting on the motivation to seek food. In PWS, ***hunger*** and ***satiety*** appear to be reduced and ***reward*** appears to be greater and may play a primary role in the hyperphagia (excessive intake). Persons with PWS, having weak "brakes", are more comfortable and safer staying away from "hills" (access to food).

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Practical Considerations

Self-regulation is not new to PWS. Persons with PWS must regulate their impulses all the time. They self-regulate when they do not grab food off your plate. They self-regulate when they accept a disappointment without a meltdown. They self-regulate when they know they are being watched. They self-regulate when they put in their daily exercise. Self-regulation is enhanced with a number strategies used by parents and caretakers over the years: clear expectations, goals, reminders, encouragement, rewards/incentives, consequences, and imminent accountability! Cognitive techniques have been used with persons with PWS to help them express their feelings, understand their disappointments, make life transitions, grieve, identify goals and steps to attain them, agree to behavioral contracts, accept their differences and work within their limitations.

But none of this comes easily. Persons with PWS do not have good judgment. They have difficulty identifying realistic long-term goals and keeping those goals in mind while they pursue the short-term steps to attain those goals. They function best when caregivers assist those executive functions by breaking down goals into manageable steps, supplying emotional support, and providing immediate rewards and consequences based upon daily behavior.

All of this comes at a cost. Self-regulation requires effort from the person with PWS and a *long term commitment* from those around him/her to provide the consistent supports needed for optimal function. The level of support required for optimal function can never be withdrawn. Optimal function will deteriorate with diminished support. Maximal function (including an individual's involvement in his or her own life decisions) requires a greater, not lesser, investment of time and effort from everyone involved in the person's care. Resources available in both the short term and the long term must be taken into account. For this reason, self-regulation and independent function are not synonymous.

For persons with PWS, uncertainty and opportunity related to food consumption are a constant source of stress. Thus, persons with PWS display anxiety and other stress symptoms when they are responsible for their own food regulation. Conversely, stress and related behavior problems can be managed by reducing uncertainty about food. This is the basic premise for the concept of FOOD SECURITY. T his term refers to the psychological state of the individual, not the presence or absence of locked access to food in the environment.

Data from the UK as well as the USA demonstrate that the maximal weight in persons with PWS frequently occurs in late adolescence and early adulthood. The major developmental task of this period is the transition from school and the parents' home to life at work and living in the community. Weight often increases rapidly during this developmental phase due to the increased opportunity for food acquisition coupled with decreased supervision and environmental support. It takes time for the family and other designated caretakers to identify what level of restriction is required for the person's independent mobility, work situation, possession of money, and access to food in order to be compatible with that person's food security and weight regulation.

Persons with PWS can be content provided their expectations and their actual life experience are concordant. A discrepancy between expectations for increased independence and the inability to sustain that independence without weight gain can be a chronic source of stress. Frequently, this stress precipitates behavioral crises.

Persons with PWS are universally stress sensitive; many persons with PWS are susceptible to mood disorders including psychotic mood swings. Co-morbid psychiatric disorders are common in PWS. These factors must be taken into account prior to any deliberate exposure of persons with PWS to an increased access to food.

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Practical Applications

1. The Principles of FOOD SECURITY ("No doubt, no hope, no disappointment") can provide a working paradigm for evaluating a person's capacity for self-regulation. FOOD SECURITY is the psychological state of the person with respect to food. This approach requires caretakers to see food issues from the *subjective* point of view of the person with PWS. Food security requires different measures for different individuals. The strategy examines the degree to which the person's expectations about food are managed:

   - No Doubt: the person knows how much food (portion control), what kinds of food (advanced menu planning), and when (daily schedule) the food will be served.
   - No Hope: the person knows that there will be no *opportunity* to obtain additional food; this usually require the use of locks to secure food access, the use of supervision in food accessible areas or situations, and the training of caretakers on how to manage the person's opportunity to buy/ steal/pilfer/trade or manipulate others to obtain food items.
   - No Disappointment: the person does not experience an emotional let-down due to false anticipation or unfulfilled expectations about food.

   "Doubts" and "hopes" may be fact-based or not; it is their existence in the mind of the individual with PWS that matters. When these are minimized, stress is reduced, and behavior is nearly always noticeably improved.

2. Past behavior around food issues appears to be the best predictor of future behavior and provides clues to the measures that may be required to develop an individualized plan for full food security. For example, some persons may never go through garbage cans, break locks or steal, while others can be quite obstreperous in this regard. Persons who have been willing to break societal rules or go to greater lengths to obtain food may be less likely to tolerate situations in which there is a chance to access food.

3. Some degree of self-regulation in a PWS-dedicated facility is not predictive of successful adaption to a mixed residence. No other medical condition requires the long term, extremely low calorie intake required of persons with PWS. Some adults maintain their weight on as little as 600 calories per day even with an exercise program. Typical calorie needs are 1000-1200 calories per day. A mixed environment leads inevitably to exposure to the greater amounts and types of foods permitted to other residents who may be consuming twice as many calories per day as the person with PWS, even if they are themselves on a calorie restricted regimen. Mixed residences have been successful when food is inaccessible to all residents. Persons with PWS can ignore food that is truly inaccessible and never potentially accessible. Finally, failures in mixed residences are not solely due to food issues. Other cognitive and behavioral traits of PWS require programming and staff management skills frequently not needed for other handicapped individuals of similar IQ. (Clarke et al.; Dykens & Kasari; Einfeld et al. (1999).

4. Theoretically, all persons with PWS who are exposed to unsupervised and unlimited food access are at risk for gorging, choking, gastric distention and necrosis leading to rupture, shock and death (Wharton et al. 1997; Stevenson et al. 2007). It is not clear how an experimental design for self-regulation can manage or eliminate this risk, but persons with a history of gorging or with a past history of episodes of abdominal distention should be considered at special risk. If self-regulation in the presence of food is to be attempted, the amount of extra food that is potentially accessible must be limited.

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Table 1 Blunted Satiety in PWS: Behavioral Evidence in Experimental Settings
Zipf and Berntson (1987) Holland, et. al.(1993) Holland, et. al.(1995) Fieldstone, et. al. (1998) Lindgren, et. al. (2000)

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