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GROWTH HORMONE AND MORTALITY IN PRADER-WILLI SYNDROME

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INTRODUCTION

Prader-Willi syndrome (PWS) is a unique condition associated with lack of normal expression of paternal alleles in a highly imprinted region of chromosome 15q11-13. Involvement of regions encoding small nucleolar RNA (snoRNA) clusters HBII52 and, perhaps more crucially, HBII85, have been identified as particularly associated with phenotype expression.^{1,2} Minimum birth incidence has been recently estimated at ~1 in 20,000 to 30,000 and population prevalence at ~1 in 50,000 to 80,000.³⁻⁵ Fewer than 1% of cases are due to inherited mutations.

Affected individuals suffer from excessive body fat independent of weight, marked deficits in muscle mass and function, growth failure with adult short stature, osteoporosis, scoliosis, hypogonadism, acromicria, neurodevelopmental delay, hyperphagia, and cognitive defects.⁶ A variable deficiency of induced growth hormone (GH) secretion and more consistently-observed low insulin-like growth factor (IGF)-I levels are characteristic and may play a role in pathophysiology.⁷

In 2000, after nearly 15 years of favorable clinical experience, recombinant human (rh)GH became the first and, to-date, only pharmaceutical agent specifically approved for treatment of PWS. The FDA labeling states: "...for long-term treatment of pediatric patients who have growth failure due to PWS" and European

From The Editor's Desk

Yes, *GGH* has a new look to acknowledge a new era with our new sponsor, INSMED. Also, with this change we welcome 2 new distinguished colleagues to the editorial board, Dr. Roberto Lanes from Caracas and Dr. Martin Savage from London. Biographical sketches highlighting their wonderful credentials are available on the journal's website. The above mentioned changes have brought about a renewal of the journal's scope and mission that we hope will be appreciated and relished by the readers.

In this issue the lead article deals with an important current dilemma—the treatment of individuals with PWS with rhGH. Dr. Phil Lee was invited to review the mortality risks to these patients and his paper clearly presents the current status and issues. Although the data are not sufficient to fully determine patients' risks, with or without this therapy, the review was necessary. The lead article facilitates an understanding of the facts as they now stand and therefore it aids in formulating the clinical choices that need to be made when treating PWS. There clearly is a need to gather additional scientific information for a precise risk analysis in PWS that will lead to well substantiated recommendations.

The abstracts and editorial comments are also very timely, all dealing with a variety of subjects that affect patients and help elucidate important pathophysiological mechanisms ie, growth in Noonan syndrome and the role of Obestatin, a new hormone that opposes Ghrelin, among other important contributions. Altogether this issue constitutes another very successful issue of *GGH*; enjoy it and thank our new sponsor for their commitment to continuous medical education.

Sincerely,
Fima Lifshitz, MD
Editor-in-Chief

labeling states “for improvement of growth and body composition” (Genotropin®/Genotonorm®, Pfizer, New York, NY); similar approvals have been obtained worldwide for other rhGH manufacturers. Numerous beneficial effects of rhGH, including improvements in linear growth, physical appearance, functional muscle mass, and infant neurodevelopment have been observed in children with PWS.⁷⁻¹⁰ Treatment of adult PWS patients with rhGH is under investigation.¹¹

In the nearly 20 years since the first reported use of rhGH in PWS, remarkably few adverse effects have been reported.^{8,9} One case of intracranial hypertension¹² and a few cases of asymptomatic fluid retention¹⁰ have been reported. Exacerbation of hyperglycemia and type 2 diabetes mellitus has been reported, usually with preceding risk factors.⁸ Malignancy has not been reported with rhGH, although an increased risk for malignancy has been suggested for PWS without rhGH based on individual reports of various types of cancer⁶ Neuromuscular scoliosis, a common progressive condition in PWS, is not worsened by rhGH.^{6,10}

Two cases of death were reported in 2002 in children with PWS receiving rhGH.^{13,14} On January 23, 2003, the Drug and Therapeutics Committee of the Lawson Wilkins Pediatric Endocrine Society issued a statement (revised May 20, 2003) including 5 additional cases (www.lwpes.org). On April 30, 2003, Pharmacia (now, Pfizer) applied a warning label to its rhGH, Genotropin, followed by a letter to health care professionals dated May 30, 2003 (approved by the FDA on October 31, 2003) stating that “Growth hormone is contraindicated in patients with Prader-Willi syndrome who are severely obese or have severe respiratory impairment.” In 2004, other manufacturers were required to add this warning to their rhGH products.

While the application of this warning was prudent in many respects, it has also led to considerable concern and confusion regarding the safety of rhGH in PWS. As a member of the Prader-Willi Syndrome Association USA (PWSA) Scientific Advisory Board, this author has been made aware of several cases in which rhGH has been denied or withdrawn by the treating physician because of this warning. Since denial of rhGH may be detrimental for children with PWS, it seems equally prudent to review the evidence for and against an association of rhGH with mortality in PWS.

MORTALITY DURING rhGH THERAPY

Following the initial reports of death during rhGH, intensive investigations for additional cases were conducted by rhGH manufacturers. As of February 2003, a total of 7 cases of death during rhGH treatment had been identified; 3 of these cases were previously registered in the Kabi International Growth Study (KIGS).

At that time, a total of 675 rhGH-treated PWS cases were registered in KIGS (personal communication, Pfizer, October 3, 2003), giving an overall mortality ratio of 0.4%. Of the remaining cases in KIGS, 16% had only one recorded clinic visit while 84% (n=565) had received rhGH for a mean period of 2.4 years.

As of May 01, 2006, a total of 18 pediatric and 2 adult deaths have been identified in individuals with PWS treated with rhGH¹³⁻¹⁹ (additional information from Dr. M. Wajnrajch, Pfizer and Dr. B. Lippe, Genentech). Considering the degree of attention given to this issue, it may be assumed that these cases represent a fairly comprehensive survey of deaths within the rhGH-treated PWS population throughout most of the industrialized world. (A database project conducted by PWSA may contain a few additional cases, as discussed in the next section.)

The 2 adult cases included a 33-year-old male who had been off rhGH for 6 weeks prior to his demise and a 48-year-old male who was known to be noncompliant with rhGH therapy. One pediatric case was a victim of bathtub drowning and another had been off rhGH for 11 months prior to death. These cases do not appear to be relevant to the current concerns. One case occurred in a 3-year-old who was known to be noncompliant with rhGH therapy; this case is included in the following analyses since therapy is not confirmed to have been discontinued for a significant period prior to death (case #8 in the Table).

As detailed in the Table, the 17 remaining cases were all pediatric, 0.7 to 15.8 years of age (7.0 ± 4.3 yr) (mean \pm SD), including 13 males. Duration of rhGH ranged from 2 weeks to 2.5 years (0.57 ± 0.66 yr). Eight of 11 cases were known to be significantly overweight. The cases include 5 previously registered in postmarketing surveillance databases (KIGS-3, Genentech National Collaborative Growth Study [NCGS]-2), 1 case reported to Genentech (GEN), 4 investigated via a regulatory process known as Pharmacovigilance (PV), and 7 from the published literature and other sources. Therefore, approximately 60% of cases were detected via postmarketing surveillance databases or other reports to rhGH manufacturers, while 40% were not.

For the 16 cases for which data are available, the rhGH dose ranged from 0.10 to 0.33 mg/kg/wk (0.18 ± 0.06 mg/kg/week, mean \pm SD). Twelve of 16 cases were receiving less than the labeled dose (0.24 mg/kg/week), 2 were at this level and 2 were above this level. The Figure depicts the doses for these cases and published doses from treatment series.

For the 9 cases in which a possible contributory factor is listed, respiratory illness was listed in all cases. Eight of 17 cases were characterized by “sudden” death. Six of these had respiratory impairment preceding rhGH therapy, one

Table. Deaths During GH Treatment

Case	Year Reference*	Age(yr) Sex	Country	Duration rhGH (yr)	Dose rhGH (mg/kg/wk)	Weight***	Cause of Death****	Comments
1	1996 (KIGS)	15.8 M	Japan	0.58	0.10	BMI=46.6	acute pneumonia, respiratory failure; no autopsy	
2	1999 (NCGS)	6.8 M	USA	0.50	0.23	BMI=23.7	died in hospital no autopsy	cardiomegaly, on carbamazepine and O ₂
3	2001 (PV)	3 M	USA	0.25	0.5 mg qd** (~0.15)	>200% IBW	found dead in bed; autopsy: ? pneumonitis	asthma-on albuterol;
4	2001 (KIGS)	8-9 M	Spain	0.04 (2 wks)	0.15	BMI=38.5	acute bronchitis, respiratory failure	history of OSA, nocturnal hypoventilation
5	2001 [14]	0.7 M	Switzerland	0.20	0.18	WT 0.63SD	aspiration pneumonia; autopsy: bronchopneumonia	died 2 days after aspirating milk
6	2001 [13]	6.5 M	Switzerland	0.50	0.26	145% IBW	found dead in bed	history of snoring, OSA, large tonsils
7	2002 (KIGS)	4.7 M	USA	0.25	0.24	BMI =31.3	aspiration pneumonia, sleep apnea; no autopsy	history of OSA
8	2003 (PV)	3 F	USA	2.50	0.5 mg qd** ~0.18 noncompliant	BMI= 17.6 at 2 yr (~75 th percentile)	pneumonia	history of aspiration pneumonia
9	2003 (PV)	13 M	UK	0.42	no data	overweight	sudden death, unexplained	
10	2003 (PV)	14.6 M	UK	1.50	0.11	BMI=42.0	viral respiratory infection, respiratory and right heart failure	
11	2003 [19] (NCGS)	4.5 M	Canada	0.17	0.17	259% IBW	died during sleep; autopsy: pneumonia, left ventricular hypertrophy, subdural hematoma	history of progressive snoring, headaches
12	2003 (GEN)	10 M	USA	~0.13	0.15	BMI= 51.6	abrupt deterioration	history of albuterol use
13	2005 [16]	4.7 F	Austria	~0.13	0.24	BMI=19.5	abrupt deterioration, ? cardiorespiratory arrest at home	previous adenoidectomy; no apnea on PS; nocturnal NCPAP
14	2005 [16]	9.3	Austria	1.0, stopped 1.3, restart 0.5; total treatment=1.5 yr	0.28, restart 0.14	BMI 30.2, 27.3 after 1st rhGH, 38.5 at restart	minor respiratory infection, sudden death at home	Progressive deterioration after stopping first course of rhGH; PS-hypoventilation & apnea, noncompliant with CPAP
15	2005 [17]	3.9 F	Italy	0.30	0.33	130% IBW	sudden death, morning	adenoid hypertrophy, snoring, apnea preceding therapy
16	2005 [17]	6.3 M	Italy	0.20	0.20	144% IBW	sudden death, morning apnea	TA hypertrophy, respiratory impairment preceding rhGH, worsened during treatment
17	2005 [18]	3.9	Greece	0.58	~0.10	Severe obesity	sudden death	
Mean ± SD		7.0 ± 4.3		0.57 ± 0.66	0.18 ± 0.06			

Notes: OSA=obstructive sleep apnea, PS=polysomnography, TA=tonsillo-adenoidectomy, NCPAP=nasal CPAP

*Year of death, if known, or publication. Source: Kabi International Growth Study (KIGS), National Cooperative Growth Study (NCGS), Pharmacovigilance (PV, Pfizer), 1 case reported to Genentech (GEN)

**Weight at time of death or rhGH dose per kg were not available for these 2 cases. For the purposes of analysis, the weights in both cases were assumed to be 20 kg, giving approximate rhGH doses of 0.18 mg/kg/wk in each case.

***%IBW= percent ideal body weight. All BMI calculations are >97th percentile for age and sex, except as indicated.

****Causes of death as reported to database are usually based on clinical reports. Autopsy findings are indicated if available.

For case 14, total treatment duration of 1.5 yr and the dose at time of death (0.14) were used for the analyses in the text.

case was reported to have worsened while on rhGH (case 15), while most of the others had no known change during therapy. Inadequate details were available for several cases, and one individual was said to have been improving on rhGH without known respiratory problems (case 17). Twelve cases were known to be morbidly overweight (>200% IBW or BMI >95th percentile for age and sex), while 5 cases (5, 6, 8, 15, and 16) were apparently within normal weight guidelines for height. Autopsy data was notably lacking for most cases, and the available data do not reveal unexpected findings. Large tonsils were noted for case 6, but this was not thought by the authors to be contributory to death.¹³ Adrenal abnormalities have not been noted in the autopsied cases.

MORTALITY WITHOUT rhGH THERAPY

Premature mortality and sudden death in PWS are not new concerns; these predate rhGH treatment of PWS by many years.²⁰ In 1981, Laurance²¹ reported a series of 33 patients, of whom 24 were alive at 15 to 41 years of age, and 9 of whom had died before age 23 years. The deaths were attributed to cardiorespiratory failure.

A retrospective clinical review of 36 individuals with PWS found 10 deaths (20-49 years old) over a 10-year period.²² Respiratory or cardiorespiratory illness was identified as causative in 40% of cases. In 2003, 6 deaths (20-43 years old) were tabulated in a follow-up study of 37 non-rhGH treated individuals with PWS who had been entered into

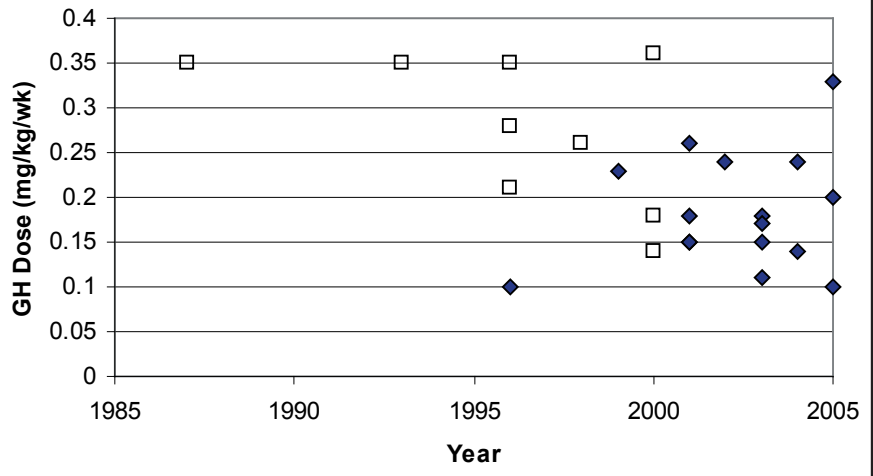
the Australian Child Development Study in 1989.²³ The calculated death rate was >4-fold higher than in a control group of 547 individuals with intellectual disability drawn from the same prospective study. A respiratory component was noted for 3 of the 4 cases for which cause-of-death was identified.

In an international summary of 27 deaths in PWS,²⁴ approximately half were related to respiratory or cardiorespiratory disease, including 9 of the 13 cases in those less than 5 years of age. Small adrenals were not observed in autopsied cases, but were noted in 3 of 4 autopsied cases in a separate review of 10 cases.²⁵ It should be noted that no functional adrenal abnormalities have been identified in PWS patients on standard biochemical testing.⁶

Support-group survey studies are limited by substantial bias, including survival and younger age. However, by virtue of their size and geographic representation, these efforts may provide valuable information regarding the characteristics of the PWS population. Nagai et al²⁶ examined the records of 494 individuals with PWS registered in 2 regional PWS support groups (2 months to 48 years of age, 46% females, 54% male). Thirteen deaths were identified (2.6% of the group, 6 female, 7 male), none had received rhGH; 7 (58%) were under 2 years of age, with deaths attributed to possible aspiration or SIDS (n=2), upper airway infection with diarrhea (n=1), cardiomyopathy with known respiratory disorder (n=1), and diarrhea (n=3). None of the infant deaths were associated with obesity. Other deaths included a 14-year-old and 20-year-old with bathtub drownings. The 4 adult deaths (23, 26, 28 and 34 years old) were attributed to cellulitis, pulmonary embolism, renal, and heart failures, respectively.

An ongoing survey of the PWSA membership (approximately 3000) has thus far revealed 190 deaths since 1977 (74% dated since 2000 [courtesy of J Heinemann, PWSA]). Mean age at death was 28 years (2 months to 63 years, 33% <21 years, 12.5% <5 years). The 14 cases reported to have received rhGH included 4 who were off therapy for several months or years, 3 with gastric perforation—a known cause of mortality in PWS,²⁷ (3 without information, and 1 each: motor vehicle accident, sepsis, severe asthma attack, and possible poor intubation (pre-existing respiratory problems). None of the cases appear to be related to rhGH, although complete analyses for some cases are pending.

Figure. GH Dose versus Year



Empty squares: rhGH doses reported in published series demonstrating rhGH efficacy.^{7,9}
Closed diamonds: Individual cases of death while on rhGH, plotted by dose at time of death and year reported (see Table).

Population-based morbidity and mortality data for PWS are not available except from regional cross-sectional surveys. Recent regional surveys in England⁵ and Belgium⁴ indicate high morbidity and mortality rates; survival past the 6th decade of life has been rarely documented. In the English study,⁵ 50% of individuals with PWS reported recurrent respiratory disease, and lifetime mortality rate was roughly estimated at 3%/yr (approximately 3 times higher than the general population). Except for these 2 population-based studies, no conclusions can be reached regarding mortality rates, and within these studies the data are insufficient to construct survival curves.

IS MORTALITY INCREASED WITH rhGH THERAPY?

Given the similarity in causes of death between the rhGH-treated and untreated cases and the apparently high underlying mortality rate at all ages in the untreated population, a logical question is whether rhGH is having a positive, negative, or neutral effect on mortality risk in PWS. The answer to this question is complicated by the lack of sufficient population-based data to construct survival curves or risk ratios. In addition, little is known about the effects of age, sex, and accompanying morbidities on mortality; information that would be crucial for estimating the additional effect of rhGH treatment.

Moreover, most clinicians are not personally familiar with the natural history of PWS, have not cared for PWS patients as a series, and are unlikely to systematically follow patients who are not rhGH-treated. There are few centralized PWS care facilities from which experiential information can be collected. Since deaths without rhGH do not engender the same level of interest as those occurring during therapy and clinical experience is limited, the casual reader or incidental PWS practitioner may have the impression that the latter represent a new and unusual series of events.

Given the lack of rigorous statistical data for epidemiologic analyses, logical models of disease causation can provide an alternate framework for consideration. For instance, at least 3 of the Evans criteria²⁸ (paraphrased for the current discussion), originally formulated for infectious diseases but often applied to other cause-and-effect associations, appear to be in doubt:

1. The prevalence of death should be significantly higher in those treated with rhGH than in those not treated:

As noted above, as of February 2003, mortality occurred in 0.4% of 675 rhGH-treated PWS cases registered in KIGS. Although this information has not been recently updated, using a conservative estimate that 1000 PWS patients have received rhGH for more than 1 year over the past 15 years and 20 deaths occurred during therapy, the death rate would be <0.2%/year. This compares to the 2.6% mortality ratio,²⁶ and 2.8% and 3%/year mortality rates^{5,22} estimated for untreated PWS individuals. Therefore, although the available data are not perfect, these suggest that mortality may not be higher in those treated with rhGH.

2. There must be a certain strength of association, eg, duration, dose-response relationship:

Higher doses do not result in increased mortality; 70% of cases were receiving rhGH doses below the labeled recommendation of 0.24 mg/kg/wk, while the published literature indicates that major PWS treatment centers are using the labeled or higher doses (Figure). In addition, higher doses were not associated with shorter duration of therapy prior to death.

Continued exposure to rhGH apparently does not continue or increase the risk of mortality. The 17 cases (Table) received rhGH for an average of 6 months (median 4 months, 2 weeks to 2.5 years). As of February 2003, the average treatment duration for 565 PWS patients in KIGS was 2.4 years, and we can assume that the numbers receiving therapy for extended periods has increased since then. However, there is no evidence for increasing numbers of deaths during longer-term therapy. In fact, the paucity of reported deaths after 1 year of rhGH provides suggestive evidence for rhGH-related reduction of the high underlying mortality rate in PWS.

Arguments have been made that the apparent early clustering of deaths represents a time-limited risk of rhGH therapy. For instance, there could be a dual effect of higher mortality in the initial phase of rhGH treatment and lower mortality thereafter, although a mechanism for the initial-phase effect has not been elucidated.

It is also possible that these 17 cases represent continuation of the natural history of the condition. At standard doses, positive effects of rhGH on respiratory parameters are particularly evident after 6 to 12 months of therapy; thereby providing a window during

the early phase of treatment during which natural history may take precedence. The situation may be as suggested in the first report: "The boy reported here...thus died before the effects of rhGH could manifest themselves."¹³

3. A coherent association should exist between rhGH treatment and death; the cause-and-effect interpretation should not conflict with the known pathology of the disease:

For the 17 cases (Table), the most commonly identified disease at time of death was respiratory failure, which is also the most commonly identified mortality association in the non-rhGH treated PWS population. There is no evidence that rhGH worsens risk for respiratory-related morbidity. In fact, rhGH has been shown to improve pulmonary function and respiratory control in PWS.²⁹⁻³¹ Since excess GH levels are associated with respiratory complications in acromegaly, it has been postulated that rhGH could cause similar problems in PWS. However, such complications in acromegaly are complex and thought to be due to a combination of soft-tissue and bone remodeling,³² changes which have not been observed in rhGH-treated pediatric populations. In addition, one might expect acromegalic airway changes at higher rhGH doses and with longer duration of therapy.

POLYSOMNOGRAPHY AND rhGH THERAPY

The involvement of respiratory compromise in the initial 7 cases of death during rhGH therapy prompted the manufacturer in April 2003 to expand the warning label on Genotropin to include: (1) severe respiratory impairment as a contraindication to therapy, (2) worsening "upper airway obstruction," including snoring, as an indication for interruption of therapy, and (3) evaluation and monitoring for sleep apnea. No statistical data in support of this sternly-worded warning label and no specific methods for assessment were presented. The result was clinical practice and liability concerns amongst clinicians accompanied by alarm amongst parents of children with PWS, primarily concerned that an approved and beneficial treatment would be withheld from their child. Many clinicians interpreted this label to mean that all children with PWS should have polysomnography and that rhGH should be withheld upon receipt of abnormal results. This was despite the fact that no relationships between polysomnographic results and morbidity or mortality in children with PWS had been identified, a population in which 0% to 100% occurrence of obstructive sleep apnea had been reported in various series.³³

After careful consideration of all available data and viewpoints, the Clinical Advisory Board of PWSA issued reasoned recommendations for sleep studies and other testing in 2003 (www.pwsausa.org).⁶ As stated: "At this time

there is no evidence of a causative link between growth hormone and the respiratory problems seen in PWS.” Several studies have shown improvements in breathing and pulmonary function in children with PWS after 6 to 12 months of rhGH.^{6,8,9,29-31} Over a much shorter rhGH treatment period of 6 weeks in a mixed group of children and adults with PWS, 19 of 25 (76%) had improved polysomnographic parameters.³⁴ A non-treatment control group was not studied and test/re-test reproducibility was not reported. Nonetheless, this latter study indicates that rhGH efficacy might be observed even over a short term. Also, in this latter study, IGF-I levels were noted to be high in 2 subjects with worsened parameters, leading the authors to postulate a role for rhGH/IGF. However, the other 4 subjects with deteriorating measures had normal IGF-I levels, and 2 subjects in the improved group had high IGF-I levels.

As of this writing, there is no evidence linking results of polysomnography with morbidity or mortality in PWS, regardless of rhGH therapy. Whether an abnormal polysomnogram itself defines morbidity is a matter for debate that is beyond the limits of this manuscript. This author concurs with recommendations that polysomnography be reserved for individuals with clinical evidence of sleep-disordered breathing or excessive daytime sleepiness, and should be preferably performed as part of a clinical research program in other cases.^{6,33} Similar guidelines may be logically applied to pulmonary function testing.

CONCLUDING PERSPECTIVES

If left untreated, PWS can be a devastating condition, with affected individuals suffering considerable physical handicap, largely related to severe lifelong hypotonia. The efficacy of rhGH, particularly in children with PWS, has provided a new outlook on life that goes beyond obvious improvements in height and somatic appearance. Against these recognized benefits are concerns that rhGH may increase mortality in the initial phase of therapy. Although conclusive data supporting or refuting this concern may or may not be available in the near future, the bulk of information reviewed above may serve as an argument against the validity of this concern.

Based on the available information, rhGH may be considered in children with PWS with prudent consideration of the following points:

1. Many deaths in infants with PWS, regardless of rhGH therapy, have been related to possible aspiration of feedings. Therefore, reflux precautions should be stringently followed until the child is ambulatory.
2. Many deaths in older children and adults with PWS, regardless of rhGH therapy, have been associated with obesity; albeit without direct demonstration of cause/effect in most cases. In addition, rhGH can exacerbate the insulin resistance associated with being overweight. Therefore, proper attention should be given to weight control.
3. Several tub-drowning deaths have occurred in individuals with PWS, regardless of rhGH treatment. Caretakers should be warned not to leave individuals with PWS unattended in a bathtub or pool.
4. Most of the reported deaths during rhGH treatment occurred with doses at or below the labeled recommendation of 0.24 mg/kg/week. Therefore, there is no apparent reason to limit the rhGH dose in relation to preventing morbidity or mortality.
5. All but one of the reported deaths during rhGH therapy occurred within the first 18 months of treatment; 82% within the first year. Therefore, clinical follow-up should be especially attentive during the first 12 to 18 months of rhGH. For patients who are not receiving rhGH, this heightened level of attention should be continual given the high inherent mortality rate.
6. There is currently no medical reason for rhGH to be conditional on the results of polysomnography or pulmonary function testing. Such testing should be considered only if clinically indicated and/or within the guidelines of a clinical research protocol.

Unfortunately, a current lack of population-based data regarding mortality and rhGH therapy in PWS prevents conclusive analyses, such as survival curves and hazard ratios, which are required to define therapeutic risk. However, assessment of current available information argues against a cause and effect relationship between rhGH treatment and mortality. Coordinated multicenter studies of treated and untreated populations are needed to bring closure to this issue. Meanwhile, in keeping with the principles of *primum non nocere* and the Doctrine of Double Effect,³⁴ each clinician involved with decisions regarding rhGH therapy of PWS should maintain an awareness of current knowledge regarding therapeutic efficacy, natural history and adverse effects to insure optimal care of individual patients.

CURRENT CONFLICTS OF INTEREST: No commercial conflicts of interest. The author has been a member of the Scientific Advisory Board of PWSA (USA) since 1992 and was previously Chair of the U.S. PWS Advisory Board for Pharmacia (later, Pfizer).
DISCUSSION OF UNLABELLED USES: none

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ABSTRACTS FROM THE LITERATURE

GH Resistance in Noonan Syndrome: From Cause to Clinical Outcome

Proportionate short stature (SS) occurs in more than 70% of individuals with Noonan syndrome (NS), an autosomal dominant disorder found in 1:1000 to 1:2500 live births. NS is also characterized by typical facial dysmorphisms and cardiac defects, especially pulmonic stenosis and hypertrophic cardiomyopathy. Although prior growth hormone (GH) studies in these patients have shown mixed results (some normal, some abnormal, some suggesting neurosecretory deficiency), in general classic GH deficiency is a rare finding.

A causative gene for NS was identified in 2001: *PTPN11* (protein tyrosine phosphatase, nonreceptor type 11), which encodes Src homology region 2-domain phosphatase-2 (SHP-2). About half of individuals with NS harbor heterozygous missense mutations of SHP-2, the majority of which involve the amino SH2 (N-SH2) or the protein tyrosine phosphatase (PTP) domains (exons 3, 8, and 13). Both N-SH2 and PTP normally interact, keeping the ubiquitously expressed, cytosolic SHP-2 in a closed, inactive conformation. SHP-2 is activated upon binding of N-SH2 to a phosphotyrosine residue, such as those on activated receptors for GH, cytokines and other growth factors. By chronically stabilizing the SHP-2 open, and hence active, conformation, the missense mutations of NS would be expected to cause gain of function of this negative regulator of receptor signaling. SHP-2 can

not only dampen signaling through dephosphorylation of the receptor itself, it can also dampen downstream signals like dephosphorylating STAT5. Thus, SHP-2 mutations would be expected to cause GH resistance in patients with NS. Three recent papers studied this proposed hypothesis.

Mild GH Resistance

Binder and colleagues recruited all 29 children who presented to their center during the past 5 years with SS and at least 3 typical anomalies of NS or pulmonic stenosis. Blood lymphocyte DNA was extracted for PCR amplification and sequencing; 11 different missense mutations of *PTPN11* were found in 16 children from 14 unrelated families (55% of patients). Of these 11 mutations, 8 occurred in exons 3, 8 or 13. Comparing the mutation-positive (mut⁺) vs mutation-negative (mut⁻) subgroups, the former were found to have a higher incidence of pulmonic stenosis (81% vs 15%) and septal defects (63% vs 15%), and younger mean age at presentation (5.1 ± 2.7 vs 10.3 ± 5.2 years). Minor anomalies and height (−3.15 ± 0.92 vs −3.01 ± 1.35 SD) did not differ significantly, and all children were approximately 1 SD shorter in height than the mean for NS. While the higher spontaneous overnight and arginine-stimulated GH levels did not reach statistical significance, insulin-like growth factor (IGF)-I (−2.03 ± 0.69 vs −1.13 ± 0.89 SD) and IGF binding protein (BP)-3