



**IPWSO**  
International  
Prader-Willi Syndrome  
Organisation

# IPWSO Health ECHO abstract

## May 18, 2021: Hyperphagia

*Please note this document is abridged from audio transcription of the Zoom session. Some errors resulting from the transcription process may be present.*

IPWSO hosts: Georgina Loughnan (GL) and Tony Holland (TH)

Presenters: Dr Tony Goldstone (TG) and Tony Holland (TH)

### Video link

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[Dr Tony Goldstone: How We Understand Hyperphagia in PWS](#)

PDF available [here](#).

### [Q&A Following Dr Tony Goldstone's Presentation](#)

**Q:** About the very early weight gain, I always think that when this occurs in young children with hyperphagia that this is because you serve the normal amount that you would for a child of this age but they do not move very much so have lower calorie needs but they eat everything you serve them, so they are getting too many calories.

**TG:** I also wonder if some of it can be GH deficiency. We haven't really had enough children having GH from under 1 year of age to see if that phase of obesity without the hyperphagia is reduced by early GH.

This is still much later than in any other genetic obesity cases. Whether the neurodevelopmental delays mean that the pathways through which the genetic abnormality in PWS has its effect is not fully mature because there is a global neurodevelopmental delay and so the structures that it's acting through mature later than normal and therefore the hyperphagia kicks in later.

**Q:** According to your results it's difficult to achieve and maintain a normal weight after the transition period. Would you recommend (care homes) in general for people with PWS?

**TG:** I gave some examples where the family home did not work but there are many situations where staying in the family home works. The patients that get referred to my clinic are often those that are failing. Families may not want to carry on caring for the child and the child may want some independence and so to leave. If either the family structure isn't working or the person with PWS is exerting some independence we have to ask where to next? In my experience there is variability. To my mind the best

treatment is a PWS specific home. That isn't to say other circumstances can't be successful but in my experience they are less effective, particularly in the cases where the person is very obese it is very difficult to affect change for weight loss.

I have not seen sustained, progressive long-term weight loss in someone who is very obese outside the specialist PWS environment. 3 reasons for that, firstly the level of knowledge about how to manage PWS in non-specialist homes is poor, secondly they are usually mixed homes and it is difficult to put in the proper structure for people with PWS without affecting the other people's access to food, thirdly the staff turnover is great in non-PWS-specific homes and we know that people with PWS need consistency and you lose the staff training. The trouble is PWS specialist homes are not available in many places.

The hope is that, while drugs won't get rid of hyperphagia altogether, the hope is they will take the edge off enough to then reduce the level of care, supervision, restriction needed. Maybe with a drug one could manage much better in a non-specialist environment.

**Q:** Interesting that children gain weight before their appetite increases. Do you think that is purely a GH effect or something else?

**TG:** We haven't done good, detailed resting energy expenditure studies over that period to really track it. It might be muscle mass deficiency but also the beginnings of hyperphagia.

**Q:** About the PC1 deficiency, I think you said it was important for the conversion of proghrelin to ghrelin, therefore if you had a deficiency in that you'd have low ghrelin. Yet people with PWs have very high ghrelin. I'm confused.

**TG:** Yes, I completely agree. That was a slide from the paper. The argument is, and this is yet to be disproven, that any measurement you do is solely dependent on your antibodies and the assay and the question is what does the antibody react to? Because the antibody could react to the precursor as well as the mature peptide. If there's very high levels of the precursor what you're detecting may be pre-proghrelin or proghrelin and there was some evidence from the Colombia group that actually in, I can't quite remember but in an assay, or blood or tissue, there were high levels of the proghrelin.

The complicating factor to that was that it's also high levels of acyl ghrelin which is the bit where the octanol groups and I don't know whether you and acylate the proghrelin.

**Q:** Yes, I thought it was the acyl ghrelin that was the physiologically active ghrelin.

**TG:** When they're measuring ghrelin. It depends what assay they're doing. The question is, can proghrelin be acylated to give you high acylated proghrelin? I doubt that. But people haven't done enough on the antibody characterisation to know.

Although they claim that could explain the high ghrelin, I don't think that's the case. We've shown that part of the reason for the high ghrelin is that people with PWS are

not as insulin resistant as you think they are going to be and we know that insulin suppresses ghrelin. One of the reasons why you don't see the reduction of ghrelin you'd normally do in obesity and PWS is because they're not as insulin resistant as they should be so they don't suppress the ghrelin. That doesn't explain why the ghrelin level is even higher than lean people.

**Q:** If it is all proghrelin we're measuring then this whole understanding of hyperphagia being related to ghrelin is wrong.

**TG:** The best study is to give the GOAT inhibitor. Completely suppress acyl levels and they have no reduction. We showed years ago in a handful of patients that if you suppress ghrelin with octreotide, you acutely get no change in food intake. So, it was never going to be the whole story.

There are caveats to that. One is, it may depend on when in development. Changes in ghrelin and leptin levels in very early development may alter hypothalamic structure so it's possible if you have high ghrelin levels from a young age that may alter the developmental hypothalamus which then predisposes to hyperphagia later on when you then suppress ghrelin. Maybe you need to be treating with drugs targeting the ghrelin system before the development of hyperphagia. Hyper ghrelin anaemia precedes the development of hyperphagia at a very early age, 2 or 3, as a way of preventing it.

Second caveat, are the downstream targets of ghrelin intact? Ghrelin is working through circuits that may be abnormal as well.

It must be said that other groups have not replicated the PC1 story in mouse models. The phenotype of PC1 deficiency due to a gene mutation is quite different from PWS but that could be a gene dosage effect. You see a lot of diabetes insipidus and GI problems in PC1 deficiency that you do not see in people with PWS.

## Poll Results

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1. Which one of the following statements best explains the hyperphagia characteristic of people with PWS? (Choose all that apply.)
  - a. People with PWS always feel hungry (2 responses)
  - b. People with PWS have an excessive appetite (5 responses)
  - c. People with PWS have a persistent desire to eat (12 responses)
  - d. None of the above (0 responses)
  
2. To what extent do you consider that adults with PWS have control over their own eating behaviour? (Indicate which one of the following statements you)
  - a. It varies from person to person but it is the same as people in the general population (1 response)

- b. It varies from person to person but all people with PWS have some control (0 responses)
- c. It varies but all people with PWS have some control but only in environments where access to food is limited (6 responses)
- d. People with PWS have very limited or no control and will always need to live in a food-controlled environment if obesity is to be prevented. (8 responses)

## Case presentation (Abridged)

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**GL:** Tony Holland is Emeritus Professor Department of Psychiatry, University of Cambridge and Consultant psychiatrist. He previously led the Cambridge Intellectual and Developmental Disabilities Research Group. Since retirement he has continued research in PWS. Since 2016 Tony has been President of IPWSO.

### Case presented:

25 years at the time of his death, male with Prader-Willi Syndrome.

Died as a result of a cardiopulmonary arrest

Treatment and significant information to date:

As an adult he had lived in different care settings including periods back at the family home. Because of his severe obesity, placement with a specialist PWS social care provider was strongly recommended but funding not agreed by the local authority (social services). Later funding was agreed but he refused to move, wanting to live closer to his family home. He moved to a temporary placement in a group home for adults with intellectual disabilities, with a room initially on the 2nd and then the 1st floor. There was poor management of his daily diet, he had limited exercise, and he refused to attend clinic follow ups. He died suddenly a few weeks after moving to this temporary placement. I provided an independent report for the coroner's hearing.

### Past medical history

Weight records indicate that he had been severely obese over many years. With changes in social care there were periods of some weight loss but this was never maintained. BMI varied between 60 and 70. He had a diagnosis of diabetes mellitus and sleep apnoea and was receiving oral medication for the former and had a CPAP machine for the latter. He was reluctant to use CPAP throughout the night.

### Physical

My information is limited to that provided by the coroner. He had regular contact with his family. Importantly, it became apparent that he was not someone with PWS who had other severe behaviours that might have made

management of his hyperphagia problematic. It seemed likely that if funding had been available for the specialist PWS placement at the time he would have accepted the offer and would have then lost weight.

## Other

This case is about learning lessons and considering how the course of someone's life could have been different.

## Questions

How can health professional influence decisions made about social care needs at an early stage so as to prevent inappropriate placements and placement breakdowns and ultimately avoid a devastating outcome?

How can and should health professionals respond when social care is inadequate?

What to do if the person with PWS does not agree to move to a PWS environment, should we ever use the law to force such a move?

### [Discussion following Tony Holland's case presentation](#)

**Q:** A comment that the specialist service they were referred to is one of ours. We assessed him and found he would be suitable and compatible and as was said, funding was refused. 8 people currently live in this service, everyone's BMI is below 30, and the oldest person there is 47.

**GL:** Sadly, we all know what works. In many countries the availability is not there and in other countries it takes so long to put the right supports in place.

**Q:** In the US where in several areas where we have plenty of group homes, it's really the funding. The cost to train staff or retain staff but to support people that are so morbidly obese, to make the case that providers need to be paid to take care of these people, many states refuse funding and many go the nursing home level care in their 20s or other non-specialist homes and you do see weight increase and deaths so there really needs to be studies that show that despite the increased costs for Prader-Willi specific homes, the benefits are far greater.

**Q:** When the patient was assessed and was granted the funding to move into a PWS specific home but at that point in time refused because he wanted to be closer to family; what's our duty of care in that situation? He's a 25-year-old man, he was PWS. We know that he needs to be in a supervised environment, particularly around food. He is refusing. I don't know how articulate this man was, how expressive in his needs. Can we overrule this decision? Do we allow freedom of choice for people with PWS or can we deny them their ability to express their opinion on where they want to live?

**TH:** He was an adult, at the time, and therefore as an adult, like all of us, he has the right to make decisions about his own life. If there is going to be a case for removing him against his consent then clearly there has to be a legal justification for that. It is a very big thing to say to someone you're going to live there, rather than there, against your will.

It will differ from country to country. In the UK there a process called the court of protection that one would go to if the person is considered to lack the capacity or understanding that allows them to make a rational choice. There are ways this can be use briskly but generally it is quite a slow and adversarial process.

It's not something we should take lightly because it is a big infringement. In this case the consequences of not doing it were catastrophic.

**TG:** Over the years, chipping away, I've usually eventually manager to get the family and the person with PWS on board. In once case the person had to get up to a BMI of 75. He is now in a group home and doing tremendously well. In this case he was very highly functioning, and he was very adamant, and had the capacity to make the decision that he wanted to be near his girlfriend, his church, his family and accepted the risks of that. It's a shame that earlier he had been willing to go a long distance away and we missed that opportunity. There was going to be a home coming closer.

Just in the last few weeks I've got another, similar case, a very highly functioning person who is on 250units of insulin a day, weight of 190kg, and he is agreeing to go into a home. I've had the CCG (Clinical Commissioning Groups, NHS England) refuse a fast-track. Thankfully social care are going to agree to fund it on an interim basis. But of he turns around once there and refuses to stay (it will be a question of if he has capacity to do so). I don't think our ability to assess capacity is easy. With this new patient I've discussed what is the most important thing in his life? He wants to be active. He wants to be able to do the things his sister does. He wants to be able to lose weight. If his behaviour is conflicting with what he says are his most important outcomes I don't think he has the capacity to make that decision and that would be our assessment. If it comes to that, saying I am refusing to be in an area that is restricting access to food it would be showing an internal contradiction and then in that case we might have to consider going to a court of protection.

I have had problems where parents refuse. I had a family where I tried for years and years and eventually they stopped coming to my clinic because they refused to hear that. It is very tricky when you've lost the connection with them. All I could do was pass it on to the GP.

**Q:** I agree what the family thinks is very important. Do the family agree? I am a bit stronger in my approach. I don't think you can force people but I don't think they necessarily have the capacity to understand (why care home intervention) is important. Particularly when a person is high-functioning, they think they are normal but they are not.

Example of 1 man who is very high-functioning, who is doing dreadfully. Every time he comes to hospital he is nearly dead on arrival. He is currently in hospital. He doesn't like the idea of being supervised. He sends me very well-written texts, he is very bright in many ways but there he just does not understand that he has to have restricted practices and there is always an excuse. They can't pick and choose and as we've heard we're very lucky to be in a country that offers this sort of accommodation. I think in this situation the parent would be glad for the respite. I think we have to be quite strong about this if we really want to do what will make the patient happy in the long term.

**Q:** But there is the risk of ostracising the patient and the family completely and then them not having treatment at all. There is the risk of slowly chipping away hoping that we reach them before the inevitable, death, happens. Is that better than forcing something where you're never going to see them again?

**Q:** If the family is on side you can handle it completely differently, and the approach is different.

**Q:** I agree it's so important to not lose our patients just because we have different opinions on how to manage best treatment. I am reminded of a case of a patient, I think she is 28 now and she came into special care over 180kg, lost weight there over 2 years, then decided she had to live on her own. She is on a higher functioning level. Left the specialist home at 78kg, and had weight gain over 8 months she is now at 145kg. I was a little angry at her because I told her this would happen and everyone predicted it. But it was so important to be there for her and not be out of touch and to allow her the opportunity to make her own experiences. She is now again willing to move into a specialist care home and I hope she will stay for longer than 2 years now.

**TH:** There is a real danger when someone with PWS refuses to do what all of us around them feel would be the best for them, that we then withdraw our care from them. They may withdraw from seeing us and that is another issue. Our responsibility is to accept that people with PWS have a life-long condition. It's not something we can treat and solve the problem. Our duty as services (and who those services should be is another issue) is to persevere and address the problems as they arise, hoping the person will then reengage and accept what everyone sees as being the right course of action.

To what extent can we use the science, what Tony Goldstone was talking about in his presentation, our understanding of the issues around food control and the problems the people with PWS have to make the case so that we can intervene earlier rather than having to wait for repeated problems over time. Can we use science here more effectively?

**TG:** An example, I have one of the few patients with the snoord116 microdeletion. BMI, when I last saw him of 55-60, no diabetes, IQ of 105. No intellectual disability whatsoever. He also had no hyperphagia anymore. There is no way he would ever accept going to a specialist residential home. He had full capacity, was completely self-caring, functioning, was just severely obese. Even if he'd had the hyperphagia I think it



would have been virtually impossible to have argued he did not have capacity. That is one end of the spectrum, there is a whole spectrum. It's very well saying no one has capacity; I think some do. Going from the science, at what point on the spectrum is there capacity and how do we assess that? When we compare it to other conditions that cause obesity and other genetic conditions, we don't always have the same severity of restrictions, so is there something special about PWS simply in its severity that means we can exert more external control? Within PWS we have to accept there is still variability.

**Q:** Comment that in Denmark it's the municipality that accepts whether the house is PWS specific or not. A client in a mixed disability home who has put on 50kg but still they won't allow a PWS home to be established. How do we as medical professionals intervene?

I am told the ruling is that she can manage in the group home. When her family takes her home, she loses weight. Last time lost 30kg and then was put back in the home and gained it back. Has diabetes, sleep apnoea. I have written several letters but the municipality denies the funds to put her in a PWS home where there is a place as mixed homes are less expensive.

**TH:** Ultimately how you might respond or the law you might use to try and affect change will vary from country to country. In a sense we must untangle where the block is, a block of understanding, or funding, of legality? I don't know how one overcomes the issue of funding other than persistence. You're often on a fine line; as it happened in this person, sudden death can occur. You're hoping to persuade people to do something before that happens. So the issues still is, how can we make the case at an early stage, particularly when someone may be transitioning from school and is perhaps willing to consider options where there is still food control?

**Q:** This person was diagnosed late, at 25, as the staff in the home asked if it could be PWS after she put on so much weight. The parents had just done what they could not knowing it was PWS. When she moved from the family home she was around 65kg and during a year she put on 50kg. My question was should we go to the law?

**TH:** Depends on what the law is in your country. It's important to state, certainly in European countries, in many countries, to force someone who is an adult to do something against their will would be unlawful.

**Q:** To the people who've worked in the area for longer, is getting a patient to accept a group home the easiest at that transition phase from adolescence to young adulthood? In my limited experience with PWS that's often a time when you see a lot of weight gain. It may be a time when, as they are moving out of school, a group environment, the concept of a group home isn't so threatening. Is that the best time to push the family to go for it?



**GL:** It depends greatly on the family. The families who exercise with their children from a very young age, they keep doing it. Those who talk about their children moving out of home just like other adults do, there is usually a much smoother transition and willingness to do it. An overwhelming number want to lose weight before and do so after admission and they see the correlation between better health.

**Q:** In this country we have guardianship orders and we have to have good grounds to have a guardian appointed and that person makes decision where there is a decision there is no capacity. We like to avoid this when we can.

**Q:** When we're talking about capacity within PWS should we be expecting someone with knowledge of PWS to undertake the assessment rather than somebody like the social working caring for that person, for example, who most likely isn't as knowledgeable as a specialist.

**TH:** In English and Welsh Law capacity is defined in a particular way. When it comes to people with PWS it is sensible to have someone who has experience in assessing capacity in people with PWS because I don't think the issues are necessarily around IQ. The issues are often around the impact of having this drive to eat, on your ability to make decisions about controlling access to food. There have been studies on POW camps that show when people are hungry they behave in ways they would not have otherwise behaved. If you have this strong desire to eat it's very hard to make decisions that mean your access to food is going to be limited.

It's interesting how many people, once they're in that environment, get angry if a member of staff doesn't stick to the rules. They want the environment but fear moving there and it's very difficult for them to anticipate what it will be like. It's not just access to food, it's also being reassured that food will be provided.

**TG:** A real problem is that of post code social work and post code funding. Whether funding assessments or capacity assessment is it a big problem if they meet a social worker who has never met anyone with PWS and is meeting them for the first time. People with PWS can sometimes be seen to be more highly functioning than they are, particularly around food. There is such a culture, particularly in social work communities of having an independent assessor.

The real problem we have with the funding is that every municipality borough acts differently in terms of funding. Some will split costs with social care and NHS care, some won't talk to each other. Does anyone know of any country where there is a national commissioning of this sort of thing? To my mind the only way this can be solved is to go to the higher-ups in the department of health and get national commissioning for specialist residential homes. The trouble is, that it is regarded still by a vast majority of people as a social placement and not the medical treatment that it is. How do we as a community and do we have a role, as IPWSO, to lobby (and we've already been to parliament) to try and change the process. I don't see it changing unless we do that.

**Q:** We're lucky in Australia to have a National Disability Service and we are able to get people into PWS home straight from 18, when they are reasonable weight. A lot of our time is spent writing letters in support of our patients. We always write to the NDIS (National Disability Insurance Scheme) and our patients get good funding and we're very successful and fortunate.

**GL:** We are fortunate to have the national disability service and a lot of people now know about PWS because we keep bombarding them with information. We use a lot of the IPWSO information and we write supporting letters and they are reviewed every year. Even that process is slow. A patient in urgent need can still take 6 months.

**TG:** What was the history of the development of that National Disability Service?

**GL:** I came about when we had a wonderful female Prime Minister. There had been talk about it for a number of years and she put it forward and it came to fruition, so we all pay tax that goes into supporting the National Disability Scheme. The idea is that when people receive these services 1 year they won't need as much the following year but we review that and let them know this is permanent. It's for all disabilities up to the age of 65. (Think) it has its own budget and it is national, not state.

## Upcoming Health ECHO sessions

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Tue 15 <sup>th</sup> June	<i>Behaviour and Mental Health</i> Tony Holland, Clinical and Academic Psychiatrist, IPWSO President
Tue 13 <sup>th</sup> July	<i>Sleep Disorders</i> Brendon Yee, Associate Professor, Respiratory and Sleep Physician
Tues 14 <sup>th</sup> Sept	<i>Diet and Exercise and the Prevention of Obesity</i> Dr Constanze Lämmer, Children's Hospital, St. Bernward Hospital, Hildesheim, Germany and Georgina Loughnan, Royal Prince Alfred Hospital, Camperdown, NSW, Australia

*Thank you very much to everyone who attended the session and participated. We look forward to seeing you on Session 5 in June.*

Ends.