Hyperphagic Short Stature. An investigation of possible genetic influences and defining the phenotype; a comparative study.

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Thesis submitted for the degree of Doctor of Philosophy

September 1996

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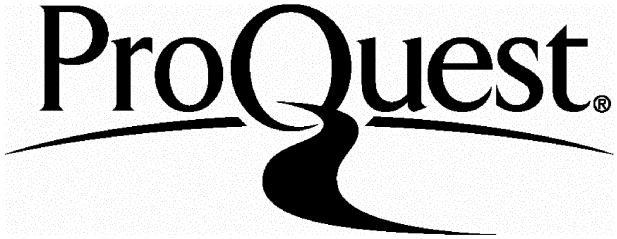

For Douglas John

Abstract:

The principal features of Hyperphagic Short Stature (HSS) are a grossly excessive appetite (hyperphagia) and short stature secondary to growth hormone insufficiency. Since a similar condition was first described by Powell et al (1967), studies have largely been descriptive, lacked appropriate comparison groups and used samples with heterogeneous aetiologies of growth failure. We aimed to refine the core features of HSS and explore possible genetic explanations for the condition.

We gathered a consecutive series of HSS affected children (n=25) (mean age 9.04 years, sd 3.78, 72% male). Second 30 children with Prader-Willi syndrome (PWS) (mean age 8.75 years, sd 2.77, 67% male) were recruited. There are many similarities between the PWS and HSS features, notably hyperphagia. Third, a consecutive series of 25 stressed (abused and/or neglected) children was recruited (mean age 10.61 years, sd 3.04, 60% male). Finally 101 siblings of the index children were assessed.

We collected parent, child and teacher reports of children's psychosocial adjustment, in addition to children's cognitive profiles and physiological stress reactivity data. Family aggregation and molecular genetic investigations were also carried out.

The findings can be described in four categories. First, most systematic assessments showed that children with HSS were living in stressful conditions. Second, the key variables of HSS were identified, all of which had a hypothalamic substrate. Other emotional and behavioural disturbances in children with HSS were suggested to be normal reactions to psychosocial adversity. Though the degree, type and consistency of hyperphagia in HSS and PWS was comparable, there were a number of features which differentiated HSS and PWS. Third, familial aggregation was described, with 44% of HSS probands having an affected full sibling, in contrast to the comparison groups. Further, siblings with HSS had relatively poor cognitive ability and psychosocial adjustment in comparison to their unaffected siblings. Finally, we showed that the major locus associated with HSS, did not coinherit with the PWS locus at 15q11-13.

Acknowledgements:

Many thanks to:

David Skuse for his enthusiastic supervision, providing invaluable career opportunities, and for always having (or rather finding) time

Marcus Pembrey for his stimulating and thoughtful supervision

Joanne Newbolt, who worked on the project during data collection, for her complete acceptance and patience throughout many challenges

Jim Stevenson for sharing some of his vast statistical knowledge

Helen Middleton-Price for her excellent technical supervision and advice

Sally Cottrell and Jenny Jones for their laboratory expertise

The Prader-Willi Syndrome Association (UK), particularly Rosemary Johnstone and Jackie Waters

All the professionals who spent many hours putting us in touch with families, particularly Linda Voss and her team

The Child Care Consultation Team and Child Sexual Abuse Team, Great Ormond Street Hospital

The teachers who returned questionnaires and the school nurses who provided anthropometric measurements

Jenny Smith for her administrative help

Olympus Sport (Oxford St, London) who donated the aerobic step to our study

Bettina Hohnen for her unfailing support and treasured friendship, also the Chutney-Fords because it's good to talk

My parents Roma and John, sisters Carolyn and Wendy, the Broadley and Willoughby families and Thalia Ely for their encouragement and enthusiasm.

The families who took part in the study, for giving so much time and personal information

The Wellcome Trust for funding the project

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Chapter 1

1.0 Literature Review

1.1 Introduction

This literature review has a number of aims. Much of the literature describing non-organic growth retarding conditions including Hyperphagic Short Stature (HSS) is confused and, at times, contradictory. We aim to define and differentiate between various growth retarding conditions and discuss the contribution that 'stress' makes to those conditions. With those definitions clear, we outline the features of HSS. As described below HSS is associated with an excessive appetite (or hyperphagia), and so the second aim of the introduction is to clarify the nature of that appetite disturbance by comparing HSS with other appetite disturbed groups. Third, as we suggest below that HSS is a syndrome associated with environmental adversity, it is important to outline the effect of environmental adversity in the general population. Finally, because we draw parallels between HSS and Prader-Willi Syndrome (PWS), the final section of the literature review describes the current literature on PWS.

1.2 An historical perspective

Phenomena from the post world war II period until the mid 1970's were largely explained as being a result of environmental experience (Rowe,1994). The peak of scientific interest in psychosocially induced growth failure, indicated by the number of publications on the subject, was in the late 60's and early 70's. Therefore most researchers with an interest in these conditions during that time may have looked to the environment as an explanation. Environmental ideas did dominate in the literature during that time period, though as discussed below, according to some authors of the time, the environment was not the sole explanation.

Recently a specific type of psychosocially induced growth failure has been reintroduced in the literature and identified as Hyperphagic Short Stature (Skuse, Albanese, Stanhope, Gilmour and Voss 1996) . With that renewed interest, current researchers view the condition through the prevailing perspective in the scientific community today. Environmental influences continue to provide explanations for psychopatholgy and physical conditions but in addition, genetic factors and gene

environment interactions are also considered as possible contributory factors. It is with this multi-factorial view that Hyperphagic Short Stature is re-examined.

1.3 Growth and stress

1.3.1 Growth patterns

1.3.1.1 Normal growth patterns

Linear growth falls into three distinct phases: the infancy stage (from birth until about the age of 36 months) during which the accelerated growth observed in the foetal period tails off. Second, middle childhood during which growth is relatively slow and third, the adolescent growth spurt, after which linear growth is complete. These three stages are largely driven by separate factors. In infancy nutrition is crucial to growth, in childhood growth and thyroid hormones are central, and in adolescence sex hormones drive the growth spurt (Karlberg, Jalil, Lam, Low and Yeung ,1994). The current study will focus on middle childhood, during which the normal expected growth rates each year are about 5 to 7.5 cm increase in height and 2 to 2.5 kilograms in weight gain (Woolston,1991).

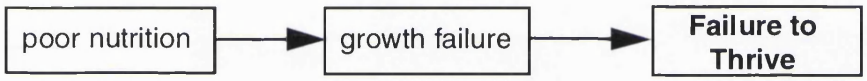
Poor nutrition (eg Allen, 1994) organic endocrine disturbances (eg Woolston,1991) or psychosocial stress (eg Skuse, Albanese, Stanhope, Gilmour and Voss, 1996) can influence growth patterns. In reviewing the literature we aim to examine in particular, the influence of two environmental factors on growth - nutrition and psychosocial stress. Skuse (1985) notes that there is a third factor that should be considered in examining the influences on growth. The third factor is each child's congenital features. The relative contribution that each of these factors makes to growth patterns in infants and children is controversial. Some argue that nutrition is invariably the cause of poor growth in infancy and childhood, others believe that children in stressful circumstances fail to grow, despite adequate calories. This means that stress has an independent influence upon growth. In this review we aim to show that the relative independent contribution of nutrition and stress on growth failure may depend on individual child characteristics. We review the literature for the normal population and consider distinct groups within that population.

1.3.1.2 Definitions of growth failure

In this chapter the literature is reviewed concerning the effects of environmental factors on growth patterns. Much of the pertinent literature is over 20 years old. There are methodological difficulties with many of the studies, with most lacking an appropriate comparison group, for example. Further, many studies use the same label to describe different conditions and therefore drawing accurate conclusions from the literature can be problematic. Because there is such confusion in the literature, it is important that definitions are clear in this thesis. There are four groups discussed below with a model describing the mechanism suggested to cause growth retardation in each of the four cases.

1) The first group are infants who fail to grow. These infants are referred to here as *failing to thrive.* Evidence suggests that, for *most* of the infants who fail to thrive, poor nutrition is the cause.

Figure 1.3.1.1: The mechanisms of Failure to Thrive:

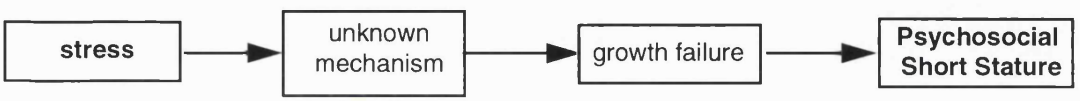


2) The second group are children who do not eat because they are living in adverse conditions and therefore feel distressed and less inclined to eat. Less commonly, children in adverse conditions may be not provided with adequate nutrition. These children are described in the present study as *anorexic*, or *malnourished* children.

Figure 1.3.1 2: The mechanisms of malnutrition and anorexia

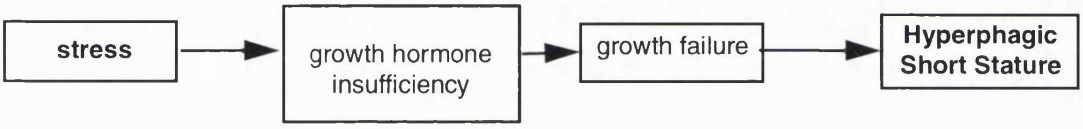
3) Third, there are children who fail to grow, with no evidence of malnutrition, in stressful circumstances. This condition is termed in the present study *Psychosocial Short Stature.* The mechanism by which the growth failure occurs in these cases is not known, but poor nutrition is not the cause.

Figure 1.3.1.3: The mechanisms of Psychosocial Short Stature



4) Finally, there are children who fail to grow in stressful circumstances, with no evidence of malnutrition. These children have growth hormone insufficiency which recovers extremely rapidly on removal from the stressful environment and they also have a distinctive appetite disturbance - hyperphagia. Children with this condition have *Hyperphagic Short Stature*. This condition was labelled as 'Hyperphagic Short Stature in 1996 (Skuse et al) but various researchers have described a similar condition which we have labelled *retrospectively* as Hyperphagic Short Stature. However the studies previous to 1996 did not use the term Hyperphagic Short Stature. In this case stress seem to impinge directly on the endocrine system causing growth failure.

Figure 1.3.1.4: The mechanisms of Hyperphagic Short Stature:



1.3.2 Failure to thrive in infancy

There has been debate in the literature about the precise mechanism by which infants fail to thrive but the current consensus seems to show that infants who have non-organic growth failure, do so in most cases because of inadequate nutrition. This fits well with Karlberg et al's (1994) observation that growth in infancy is largely driven by nutrition. The most rigorous study was carried out by Whitten, Marvin, Pettit, Fischhoff (1969) who aimed to study objectively whether infants fail to grow, *despite* adequate calories. They describe 'maternally deprived' infants with no organic cause for their failure to thrive. 13 infants were deliberately exposed to conditions of deprivation during a hospital admission, but they were fed adequate calories (condition 1). 6 infants from this group were then fed the same diet but for two weeks they were appropriately stimulated (condition 2). A sub-group of four infants who had been in hospital were followed-up at home, after hospital discharge. Food was delivered to their home, mothers fed the infant and were observed. Food uneaten by the infant was recorded. No feeding guidance was given by professionals (condition 3).

In condition 1, 10 of 13 infants showed weight gain above the 50th centile. In other words adequate calories were enough, in a poor environment, to foster a relatively good growth rate. Condition 2 included two infants who had thrived in condition 1 and two who had not. The two thriving infants continued to thrive when well nourished and stimulated, the two infants who failed to thrive continued to do so despite the positive conditions. 10 children were returned home, 4 of these were observed in condition 3. These children gained weight at an accelerated rate, in 2 of 4 cases greater than that achieved during hospital under-stimulation and far exceeded the rate recorded pre admission.

Whitten's team believe that psychological factors had been previously attributed as the direct cause for poor weight gain in some studies, when in fact inadequate calories were the cause. They note that 7 infants in 'maternally deprived' circumstances gained weight when the calorie intake was being objectively assessed. This study is to be applauded for meticulously recording the amount of calories ingested as opposed to the amount offered to infants. It would be ethically unacceptable to increase the experimental deprivation condition, but chronic deprivation as opposed to that lasting only two weeks would provide additional evidence that growth failure is a nutrition issue in infancy. There is one additional concern. Two of the infants failed to grow in the sensory deprived condition (though they also showed poor growth in condition 2). It may be that there was an undiagnosed organic cause for their growth failure, or it may be that these particular infants were failing to grow via another mechanism. Whitten's team suggest that maternal deprivation may lead to anorexia in a child, as opposed to 'obstructing' weight gain despite adequate calories. Two of these infants had been force fed by their mothers, an experience that would almost certainly cause an aversion to eating in the child subsequently.

For many infants poor nutrition and other psychosocial stress coexist. Kreiger & Sargent (1967) also describe 35 infants who showed growth failure secondary to malnutrition, 60% had been deprived of sensory stimulation and therefore neglected at home. It seems a fair conclusion that for most infants who have non-organic failure to thrive, poor nutrition is the cause.

Though nutritional explanations are appropriate for most infants, Benoit (1993) notes that there may be individual differences in infants, affecting metabolism or ingestion in infants, which may complicate the picture.

Skuse et al (1994) note that within an epidemiological sample, there were two distinct groups of failure to thrive infants, children who failed to thrive before six months and those who failed to thrive after that period. The two groups were distinct on a number of environmental variables. The 'late' failure to thrive group families reported poorer social support, less financial stability (though earning comparable amounts to the other group), lower maternal cognitive ability and greater psychiatric disturbance, though there was no detectable difference in early feeding or weaning patterns in either group. Such a finding may lead us to suspect that different environmental factors interact with individual infant characteristics in some cases of infantile growth retardation.

Summary

- Poor nutrition causes most cases of infant non-organic failure to thrive
- Other psychosocial adversities, such as neglect, are often observed in malnourished infants
- It is possible that environmental factors may influence some infants who show failure to thrive in different ways, depending on individual infant characteristics.

1.3.3 Malnutrition and anorexia in childhood:

As in infancy, during childhood poor nutrition results in poor growth, but as Karlberg et al (1994) discussed, nutrition is not the key factor in growth failure during middle childhood. Poor nutrition in middle childhood can be a result of anorexia (or food refusal), in addition to a lack of adequate food provision such as described in conditions of socio-economic deprivation. Lack of adequate calorie *provision* as opposed to ingestion may be more frequent in infancy than in childhood. This is of course partly because children are more mobile, independent and more able to articulate their needs than infants.

Though Sandberg, Smith, Fornari, Goldstein & Lifshitz, (1991) do not describe psychosocial adversity in their study, they demonstrate the influence of nutrition in a group of short children with 'nutritional dwarfing' (ND) . They suggest that short stature and poor growth velocity can be secondary to a 'self-selected hypocaloric diet'. These children do not have anorexia nervosa or bulimia as there is no body image distortion. According to Sandberg et al then, there are some children who do

not wish to eat adequate amounts. The reasons for such behaviour are open to debate.

Children in psychosocial adversity may show growth retardation

Other studies seem to illustrate directly that emotional stress may impinge on appetite. These children develop growth failure because stress and nutrition are interacting. In other words, some children do not wish to eat because they feel distressed. Widdowson (1951) described two orphanages during the 1940's, during which rationing continued. She described 'official rations,' indicating that both orphanages were matched in terms of the nutrition children were *offered*. Both groups of 50 children in each group, aged between 4 and 14 years, were under-weight and short, though one group were failing to thrive to a greater degree than the other. Orphanage A had a 'stern and forbidding' matron, the other, orphanage B had a matron who seemed fond of the children. Children under the 'positive regime' consistently put on more weight and grew along a higher growth chart centile than those in orphanage A.

Weight in particular, and height to a lesser extent were described by Widdowson as responsive to the environment. Bear in mind that Waterlow (1994) noted that weight recovers before height following a period of malnutrition. Widdowson suggests that the children were eating the same amount but the 'stressed' children failed to grow. A more likely interpretation is that the children who felt intimidated by the matron were anorexic. We would suggest simply that when the environment changed their appetite recovered and their growth recovery followed. As discussed further below, there may be some children who react to stress in a distinctive way, but for most children, the stressful environment seems to influence their propensity to eat, which then influences their growth.

The same interpretation might be imposed on an interesting study by Karp, Scholl, Decker & Ebert (1989). They aimed to document whether children from poor communities are better nourished than abused children from the same environment. There were 196 children, 53 of whom were physically abused, aged between 2 and 6 years old. Growth retardation criteria were defined using Waterlow, Buzina, Keller, Lane, Nichaman and Tanner (1977) standards eg height below the 5th centile (stunting) and weight for height below the 5th centile (wasting). Waterlow et al (1977) notes that wasting is the first sign of malnutrition. In chronic malnutrition there is

stunting as the weight for height ratio returns to normal - where there is both acute and chronic malnutrition there will be both wasting and stunting.

Karp et al (1989) report that abused children were significantly more likely to show wasting than the non-abused children, similar to that seen in acute malnutrition (16% vs 0.7%) but there were no significant differences between the abused and non-abused population in terms of stunting. None of the sample were both stunted and wasted. Both groups of children seem to have access to the same nutrition according to the authors. We would argue that some children from the general population, when they are stressed (in this case abused), feel less inclined to eat and as a consequence are showing signs of acute malnutrition.

Taitz & King (1988) also described the growth velocity patterns in children who had been abused. They note that simply using centiles for height and weight to define failure to grow may exclude children who demonstrate poor growth velocity. 260 abused children were studied. Children were identified as having a growth problem if their weight or height was -2 sds below the population mean or if they showed catch-up or fall in growth velocity of at least 0.5 sds Using these criteria, 71 children were growth retarded, 43 having impaired linear growth. 39 were at least 2 sds below the population mean in terms of height. Unfortunately there was no comparison group or discussion in the study about the influence of puberty on the children's growth trajectories. These data might suggest that chronic anorexia in the context of stress is not a universal reaction, but rather one that is relatively common as 43 children were showing growth failure from a population of 260.

11 of these children were removed from home and 10 showed 'catch-up growth' of at least 0.5 sds. Of the 28 growth retarded children who remained at home, 2 showed catch-up when a new father figure appeared. A further two children, who experienced no apparent environmental changes, showed a similar recovery but the remaining 24 demonstrated no such recovery in their unchanged environment.

It is most likely that the 'catch-up' growth was as a consequence of appetite recovery. However the study included some children within the series who seem rather distinctive, for whom nutrition alone may not be the key to growth failure. One child showed dramatic *height* catch-up for several months before a similar improvement in weight was seen. Children who are recovering from malnourishment gain weight first before height (Waterlow, 1994). This suggests that nutrition may

not have been the cause of this particular child's growth failure. Such cases will be discussed further below.

Summary

- Emotional stress may influence weight gain and linear growth in some children in the normal population because they feel disinclined to eat. There is nothing 'wrong' with these children in terms of their organic health.

Children with non-organic growth failure are often living in psychosocial adversity

We describe a group of children below who are not identified on the basis of their stressful experiences, but due to their growth failure. However, psychosocial adversity is usually described in addition. For these children too, malnutrition is almost certainly a causative factor in their growth retardation.

Pollitt & Eichler (1976) described 19 children aged 1 to 5 years old, who had non-organic growth failure. They were compared to 19 age, sex and race matched controls. Unfortunately no matching was made on the basis of socio-economic status. Case inclusion criteria were: height and weight below the 3rd centile, normal birth weight and gestation age and no organic cause for their growth retardation. The authors carried out an intensive study of behaviour with home visits made each week for 11 weeks. Family relationships in the case group were poorer than those described in the control group, for example physical punishment was used more often on case children.

Case children showed significantly more feeding problems in infancy, ate fewer calories and had a poorer response to food. The study is rather difficult to interpret as they note that the case children may have eaten fewer calories simply because they were shorter, rather than being stunted due to fewer calories. However it seems likely that poor nutrition was contributing to their short stature.

Schutt-Aine, Drash & Kenny (1973) describe 3 cases of children who were 'maternally deprived'. The group described had elevated growth hormone levels in comparison to a group of 11 comparison children (growth hormone mean of 16 nmg/ml as compared to 8 nmg/ml respectively). As their growth hormone was elevated, this strongly indicates that the children were malnourished (Woolston,1991).

Another example of growth failure secondary to malnourishment in conditions of psychosocial stress is the study by Kreiger and Good (1970) who describe a series of children who, on the basis of physiological data, were shown to be suffering from malnutrition.

Summary

- Children recruited on the basis of their short stature are often malnourished. This is almost certainly the cause of their growth failure.
- Children who are malnourished are often described as living in psychosocial adversity.
- It is possible that the psychosocial adversity may cause emotional stress, leading to anorexia and consequent growth failure.

Stress and growth failure are not invariably associated with malnutrition

There are also studies in which the children living in stressful circumstances such as abuse or neglect show growth failure, in which malnutrition may not be the entire explanation. This suggests that stress alone, even without malnutrition can cause growth failure. The data described below are rather confused but do raise questions about the influence of malnutrition in psychosocially induced growth failure.

Talbot, Sobel, Burke, Lindemann & Kaufman (1947) described a group of 28 boys and 23 girls aged between 2 and 15 years who were of short stature with no organic cause. The nutritional intake of each child was assessed by taking a history. 85% of the sample had a calorie intake that was at the lowest limit for normal intake for children of equivalent chronological age though the authors made no allowance for the effect of short stature. They describe environmental difficulties in approximately 70% of cases. The authors list the environmental concerns, noting 'mental deficiency in the parent' or 'child rejection' . They suggest that the short children in the sample who were under-weight were significantly more likely to live in stressful circumstances. However it is noteworthy that here there is evidence that growth failure cannot entirely be a consequence of malnutrition as the children were in some cases at the expected weight for height and showed growth hormone deficiency. Malnourished children showed elevated levels of growth hormone (Woolston,1991). It seems that malnutrition cannot account for all cases of growth failure. There may be an independent influence from another source.

Apley, Davies, Davis & Silk, (1971) also describe 16 patients, under the 3rd centile for height, with no physical cause for their short stature. Of the 12 cases investigated, all had normal growth hormone levels which strongly suggests that they were not severely malnourished. However Pollitt and Eichler report that the majority of children were described by their parents as poor eaters, indeed dietary analysis revealed that it was deficient in 11 cases. Poor family relationships and social support was common to all cases. Malnutrition may be part of the explanation in these cases, but it may not account of all the cases in these studies' series.

Can stress impinge directly on growth failure?

MacCarthy (1974) notes that there are certainly children who fail to grow due to poor nutrition, but similarly there are short children in stressful circumstances who do not appear to be under-nourished. Further Dubowitz, Zuckerman, Bithoney and Newberger (1989) note that children with growth failure must be treated with a multi-factorial approach because that is the nature of the aetiology. In other words psychosocial stress may be an important contributory factor acting independently on growth, not simply through poor nutrition for some children. MacCarthy (1981) notes that in infants growth failure is most often due to inadequate calories, but that in older children, there may be, for some children a 'pure' psychological effect on growth and the endocrine system. We would also argue there are some children in which there is little or no evidence of malnutrition. Benoit (1993) notes the importance of psychosocial factors in growth failure. She suggests that all children do not fail to grow simply due to malnourishment or food refusal. MacCarthy (1981) reviews the evidence and suggests that though some children with 'deprivation syndromes' do show evidence of malnourishment, equally there are many who do not. These cases, he suggests are 'a separate category ... of the syndrome'.

Summary:

- Many 'normal' children who live in stressful circumstances may show growth failure as a consequence of poor diet provision or perhaps most likely as a result of food refusal. This is a view held by Rutter (1972) .
- Other children are characteristic in terms of their poor growth, in whom malnutrition continues to play a part, and who are also described as living in stressful circumstances.

- It is possible that these two groups are homogenous but recruited from different sources, the first on the basis of stress and the second on the basis of growth failure.
- There are some children who fail to grow, but in whom malnutrition is almost certainly not the central feature. Stress may disrupt the growth mechanism, independent of malnutrition

1.3.4 Psychosocial Short Stature

For the purposes of this thesis, children who have growth failure, in which malnutrition is excluded, but who respond to psychosocial adversity with growth retardation are regarded as having 'Psychosocial Short Stature' (PSS). Children with growth failure and high growth hormone levels or physical evidence of malnutrition are therefore excluded from the diagnosis of PSS. The characteristics of these children are described below. For example Skuse et al (1996) note that 26% of a growth retarded group, with no organic cause for their short stature appeared well nourished but living in conditions of stress. These children have PSS. We don't know the cause of such environmental growth failure, but lack of calories is apparently not the explanation. There are a number of other studies in the existing literature describing such a group.

Conditions of stress seem invariably associated with the identification of PSS. Patton & Gardner (1962) describe a series of children, whom we would regard as having PSS . All affected children were living at home in conditions of chronic intra-familial stress. Money, Wolff & Annecillo (1972) also describe a classic series of PSS cases. 75% of the children were noted to have a physical injury on admission to hospital and there was evidence of severe physical punishment in 69% of cases. Money, Annecillo & Lobato (1990) describe 16 cases who had suffered from PSS in childhood, most of whom had been sexually abused. Guilhaume, Benoit,Gourmelen & Richardet (1982) described a series of children with PSS, in which all the children had experienced emotional and psychological deprivation.

1.3.4.1 Physiology

Talbot, Sobel, Burke, Lindemann & Kaufman (1947) describe a sample of 8 children (4 were underweight who may be anorexic and 4 of normal weight, whom we might regard as being PSS) who were given a substitute growth hormone for 3 months. All children showed an improved growth rate during administration of the drug, despite

there being no change in their diet. This suggests that children with PSS may respond to exogenous growth hormone administration.

1.3.4.2 Physical features

In terms of physical features, children with PSS are described as having delayed bone age (Patton & Gardner, 1962) and delayed puberty (Money and Wolff ,1974) according to Tanner Whitehouse standards (1976). Money and Wolff also suggest that there is a relationship between the time spent in the stressful environment and the degree of delay in puberty, but no analyses are performed to support this argument.

1.3.4.3. Cognitive features

Cognitive deficits are also described frequently in association with PSS (eg Patton and Gardner, 1962)

1.3.4.4. Neurological features

There is evidence that children with PSS have disrupted sleep patterns. Wolff & Money (1973) describe sleep disturbance in 20 PSS cases using parental report. Poor sleep was defined as taking more than 30 minutes to fall asleep or getting up during the night to roam the house. They found a positive correlation between poor sleep and poor growth. Further growth velocity was significantly greater during periods of good, as opposed to poor sleep. But, as the authors note, the relationship is one of association rather than causation.

There is also objective evidence, in addition to parental reports, of abnormal sleep architecture. Guilhaume, Benoit, Gourmelen & Richardet (1982) describe the sleep architecture of 4 PSS cases, using polygraphic sleep recordings. Cases were aged between 1 and 3 years, and there were 4 healthy comparison children of a similar age. All four cases showed a deficiency of stage IV sleep on admission to hospital. They note that though some aspects of abnormal sleep architecture are present in other childhood sleep disorders, the stage IV deficits are specific to this condition. It has been reported in adult depression, though not in children with major depression (Puig-Antich, Gotez, Hanlon, Davies, Tompson, Chambers, Tabrizi and Weitzman, 1982) . The authors suggest tentatively that slow wave sleep disturbance may have a casual link with PSS. There is, at least in theory, a valid reason to explain why children with PSS should have abnormal sleep architecture, as growth

hormone is released primarily during stage IV sleep (eg Friess, Wiedemann, Steiger and Holsboer, 1995 for review).

Taylor and Brook (1986), while providing further evidence that PSS is associated with relative deficits of stage IV sleep, also highlight a crucial point. They showed that children with growth failure due to poor nutrition did *not* show stage IV sleep deficits. This supports the theory that children with PSS may be growth retarded, in the context of stress, but are not malnourished.

1.3.4.5. Reversibility of growth hormone production?

In the literature, the reversibility of PSS's features in response to a change in environment is often described as characteristic of the syndrome. This means that children suffering from PSS in the context of stress, will show recovery in the form of catch-up growth following separation from the stressor. Reversibility of growth hormone insufficiency after removal from the stressful environment is thought to be the mechanism by which growth recovery takes place. Indeed the condition is sometimes referred to as 'reversible somatotropin deficiency' (Wolff and Money, 1973). It may be true to say that physical catch-up growth is observed in PSS, however recent data provided by Skuse et al (1996) show that growth hormone level reversibility in response to the environment *only* applies to a distinct group of children.

Skuse et al (1996) identified a core group of children with a syndrome we have termed Hyperphagic Short Stature (HSS). Children with HSS are distinct from PSS on the basis of their hyperphagia (or excessive appetite) and other features described more fully below. Skuse et al (1996) have shown that *only* children who are identified as having HSS will show growth hormone level reversibility within days of being separated from the stressor. They describe over-night growth hormone profiles for a group of children with anorexia, PSS and HSS on day one of admission to hospital and then on average after 18 days in hospital. During their hospital admission children were separated from the stressor, which was most often intra-familial abuse. Children with HSS showed growth hormone reversibly during the 18 day period, anorexic and PSS affected children did not.

Further, children with HSS show physical catch-up growth which is extremely rapid and in which height recovers before weight, which one would not expect in malnutrition (Waterlow, 1994). We suggest that it is feasible that children with PSS

show catch-up growth in response to environmental improvement but the mechanism by which this happens seems to be different from HSS. We would regard children with HSS as distinct from children with PSS, and those with growth failure secondary to malnutrition. HSS affected children show rapid catch-up growth following growth hormone levels increasing from sub to supra-normal levels in response to a relatively stress-free environment.

The children with HSS are at the centre of this thesis. The definition and history of 'true' HSS will be described below but the key point here is that PSS and HSS (as well as children with growth failure secondary to malnutrition) are presented in the existing literature as an homogeneous sample. As a result of this, some of the features (such as growth hormone reversibility) which are described as being characteristic of PSS, may actually only be characteristic of HSS, depending on the proportion of HSS affected children in the whole sample. Many samples do not identify whether their sample are hyperphagic or not. It is impossible in some cases to partial out the PSS and HSS characteristics from existing literature. The review below highlights this problem.

1.3.5 Nutritional growth failure, PSS and HSS confused

Albanese, Hamill, Jones, Skuse, Mathews & Stanhope (1994) described 11 well nourished children aged between 2 and 13 years. All children were living in circumstances of psychosocial adversity, and six of the children were found to have been sexually abused and identified in their study as having 'PSS'. However with the benefit of data from the Skuse et al (1996) paper, it is clear that the sample was not an homogeneous group. Some children were HSS, others were not. The group mean showed growth hormone reversibility during hospital admission, but only those individual children within the sample we would *now* identify as HSS showed growth hormone (GH) level reversibility. Other children, correctly labelled as PSS did not show GH recovery from sub-normal to above normal ranges (Skuse, unpublished data). Three of the HSS affected children were placed in foster care, and presumably secondary to an environmentally induced increase in GH production, showed the rapid physical catch-up growth which we believe to be characteristic of HSS. Because we are able to re-examine existing data with the HSS vs PSS distinction in mind, the potentially confounding factors which may be inherent in other existing studies are clear.

For example, Patton & Gardner (1962) describe 6 children with growth failure secondary to maternal deprivation. Only one child according to the behavioural description can be regarded as having HSS, the remainder were probably PSS. Of the six children, one showed rapid catch-up growth in response to a change in the environment, while the others showed a 'favourable response' but they do not specify any further. We cannot tell from the data presented whether the same child who had HSS was also the child who showed rapid catch-up growth, but it is a tempting possibility. Further Pollitt and Eichler (1976) described 19 children with growth failure, some of whom had nutritional deficits, others seem to have PSS in which malnutrition was not the key. One child, according to their description we would now label retrospectively as a 'true HSS case'. The authors note that it was this hyperphagic child who had a distinctive disrupted sleep pattern. Kreiger and Mellinger (1971) report a series of children who they suggest have 'deprivation syndrome'. They note that some of the series were growth hormone deficient and hyperphagic (we would predict that these were the true HSS cases) and some of the group in which there was a confirmed nutritional deficit had *elevated* growth hormone levels. It is likely that the inconsistent pituitary function tests in the group are because the sample was heterogeneous in terms of their aetiology.

Many studies do not specify whether or if children within their sample are hyperphagic or not. Guilhaume et al's study (1982) is reviewed above. They describe some of their series as having reversible growth hormone production following admission to hospital. They do not describe the children's behaviour that might allow us to identify HSS or PSS, but on the basis of the Skuse et al paper (1996), one might assume that they are HSS as opposed to PSS. MacCarthy (1981) recognises that some growth retarded children are hyperphagic and other refuse food, but suggests that they have the same aetiology, a hypothalamic disorder. We would suggest that the conditions have distinct aetiologies.

Woolston (1991) notes that there is chaos in the literature - children with 'failure to thrive' in which there are nutritional deficits are confused with children whom we have retrospectively labelled as having HSS, 'although these children (with HSS) represent a clearly defined diagnostic syndrome....their symptoms are persistently confused with those of failure to thrive'. We would also argue that HSS cannot be regarded as being on the same dimension as any other non-organic growth failure, including PSS. It should be regarded as distinct in terms of aetiology, behaviour, physiology and possible mechanisms.

Below the literature is reviewed concerning children who have HSS as opposed to PSS, anorexia or malnutrition. The judgement about true HSS caseness was made by the present author *retrospectively* from the clinical descriptions of the children in existing literature. The authors of the previous studies (with the exception of Skuse et al, 1996) did not used the term HSS, but we have applied that label to the children because they appear to fit the HSS diagnostic algorithm. It is important that the same label is used for the same condition. There remains the possibility that pertinent HSS literature is not discussed in this section if previous authors omitted descriptions of hyperphagia in their sample.

1.3.6. The features of HSS

HSS can be summarised using four concepts:

- growth failure
- hyperphagia
- stress
- reversibility

These key features, and others which are often described in association are illustrated below.

In 1967 Powell, Brasel, Raiti and Blizzard described 'emotional deprivation and growth retardation'. They described the core features of a condition that we have recently termed HSS. But it was Skuse et al (1996) who drew attention to the key variable of hyperphagia or appetite disturbance in the prediction of growth hormone reversibility in response to environmental change. Using the Powell et al (1967a & b) and Skuse et al (1996) articles we discuss HSS. Descriptions from other studies of children who seem to have the condition that we have recently identified as HSS are also included in this section.

1.3.6.1 Anthropometric features

Short stature or poor growth velocity, is by definition, observed in HSS. Powell et al (1967a & b) note that all the children in their series were short, with heights between 30% and 60% of chronological age. Skuse et al (1996) found that children with HSS and children with other types of psychosocially induced growth failure were equivalent in terms of the severity of growth retardation. Severe growth retardation

is also reported in all other studies describing HSS. For example, Mouridsen & Nielsen (1990) describe an HSS affected child whose height was below the 3rd centile, as do Green, Schur & Lipkowitz (1959) and Money (1977). Proportional weight for height is also reported in HSS, for example by Skuse et al (1996), Money (1977) and Mouridsen & Nielsen (1990) and Bowden & Hopwood (1982) for example. This is important as a low body mass index suggests malnutrition may be a contributory factor.

1.3.6.2. Hyperphagia and appetite disturbance

Powell et al (1967a & b) described all their series as showing either polydipsia (excessive drinking) hyperphagia or polyphagia (which might include eating non-food substances). Stealing, foraging, hoarding of food was common as was gorging on food and vomiting. Parents described their children as eating until their stomachs were swollen and distended. Appetite disturbance (and growth retardation) seems to have begun according to parents before children were 24 months old, though not invariably. These disturbed eating patterns resolved on removal from the stressful home almost immediately. The children in the Powell et al series often woke during the night, in some cases this was in order to steal food, but this also reflected sleep disturbance as the children apparently roamed at night.

Hyperphagia (an excessive appetite) is the core feature of HSS. To emphasise the importance of appetite disturbance in the identification of the true syndrome, Skuse et al (1996) re-named the condition Hyperphagic Short Stature. Children *without* the appetite disturbance and in whom malnutrition is not a concern, must be regarded as having PSS. According to Skuse et al (1996), the features under the umbrella term of hyperphagia include: eating excessively requiring restraint, gorging and vomiting, stealing food, hoarding food, drinking excessively, pica, eating discarded food and searching for food at night. In order to be identified as hyperphagic, children in the Skuse et al series had to show at least three of these features according to a diagnostic algorithm. Using hyperphagia as the defining variable predicts growth hormone production reversibility, in addition to other features described. Blizzard & Bulatovic (1992) provide a detailed description of appetite disturbance features which mirror those described by Skuse et al (1996); polydipsia, hyperphagia, pica, stealing food, eating discarded food, night roaming, gorging and vomiting. But they suggest that the frequency of the hyperphagic symptoms may be less common in less extreme cases. We would argue that

absence of hyperphagia indicates the qualitatively distinct PSS, or anorexia rather than a less severe form of HSS.

It is striking how consistent the reports of hyperphagia are in the existing literature. For example Mouridsen & Nielsen (1990) describe classic behavioural features of true HSS, hyperphagia and pica. Swanson (1994) discusses a case presentation of HSS in a 6 years old girl who was adopted at 11 months old. She was scape-goated by her adoptive parents. They required her to eat in her own room, away from the family because they found her eating habits so repulsive, this is commonly reported in HSS in our experience. She demonstrated hyperphagia and polydipsia consistently.

Bowden & Hopwood (1982) describe a population of 10 children aged between 2 and 14 years. 90% of the sample had an eating disorder (which is almost certainly hyperphagia) and 40% a 'drinking disorder' (or polydipsia) which meant, for example, drinking from unusual sources such as ditch water. Further they note that the children who were hyperphagic were indiscriminate in terms of what they ate, which corresponds to pica and of descriptions of eating discarded food described by Skuse et al (1996) and Powell et al (1967a & b).

Money (1977) describes his series as having 'unusual eating or drinking patterns'. Green, Campbell, David, (1984) in a review of the literature note that hyperphagia and/or polydipsia should be present to make the diagnosis, as do Silver and Finkelstein (1967) who note a 'voracious appetite' as a key diagnostic feature in what they describe as 'deprivation dwarfism'. MacCarthy (1974) accounts gorging and vomiting, pica or drinking from the toilet bowl in some children. Hopwood and Becker, (1979) describe the most common behavioural disturbance in their series of growth retarded children as 'an altered relationship with food'. They list the proportion of the 35 children who showed polyphagia (86%) pica (54%), stealing food (48%), polydipsia (26%) etc. Unfortunately they include within the series, a number of children (10%) who appear under-nourished.

Reinhart & Drash, (1969) describe a female fraternal twin who displayed classic polyphagia and polydipsia, while her twin brother was unaffected either by such appetite disturbance or by growth retardation. Ferholt, Rotnem, Genel, Leonard, Carey & Hunter, (1985) suggest that 'unusual behaviour around food' was described in the majority of their cases, and excessive eating was described in 70% of children in their series.

Green, Schur & Lipkowitz (1959) also describe hyperphagia in a case study and they are unusual because they attempt to explain the behaviour observed, using a psychoanalytical theory. For example, they suggest that the child's frequent demands for food were an attempt to relieve tension, rather than due to hunger and that hyperphagia was 'a magic acting out of his wish to grow'. Our interpretation of the data are that the child has a physiological drive for food rather than unconscious motivations. The vast majority of studies are descriptive, simply documenting the existence of the behaviour without attempting to theorise about its mechanism. This is true for much of the HSS literature. There is a series of descriptive studies, with little attempt to explore the mechanisms of the condition.

1.3.6.3. Stress

Like PSS, the HSS diagnosis is strongly associated with conditions of chronic stress, most often intra-familial abuse. All the children in the Powell et al (1967a & b) series lived in adverse home circumstances such as experiencing emotional abuse. Skuse et al (1996) also described stress as characteristic of their HSS series. The association between stress and HSS does seem invariable in existing studies but it not documented systematically. Many children with HSS and PSS or non-specific growth failure are identified as living in stress in a post hoc manner. There is a tendency in the literature to identify the child's diagnosis and 'find' the stress thereafter. It is possible that non-specific cases of growth failure have been labelled as a reaction to stress. Other studies, while almost certainly describing a true HSS case are rather complacent about attributing the growth failure to environment adversity.

Hopwood and Becker (1979) describe a series that was largely, but not exclusively hyperphagic. They note that there were family stresses including marital conflict and 'emotionally absent fathers' though in addition, 13 of 35 children had been physically abused. There was no systematic assessment of family relationships. The same rather post hoc assessment was made by MacCarthy & Booth (1970) who describe a series of 10 children living at home with a disturbed parent-child relationship and poor attachment. Silver and Finkelstein (1967) also describe parental psychopathology rather vaguely, for example one child had a 'strict, undemonstrative' father. They note psychological and emotional deprivation in all cases retrospectively, however they do not describe how this assessment is made.

Reinhart & Drash (1969) diagnosed HSS in fraternal twins but describe the family as 'well adjusted', noting only that there was a rather difficult relationship between mother and affected daughter but it was described as being rather mild. Green, Schur & Lipkowitz (1959) describe a sequence of events that they suggest explained one boy's growth failure. The boy's father died when he was 9 years old, he had his tonsils removed, he had been circumcised and his mother had a number pregnancies subsequent to his birth . While these events may have been transiently stressful, they are certainly not typical of the HSS condition. It may be that there was an undiscovered stressor affecting these children in addition to those described by the authors, as most other circumstances in which the HSS affected children live are severely and *perpetually* aversive.

Money (1977) described a traumatic case of a child who lived in physically and emotionally abusive conditions for 16 years. The boy had been isolated to such a degree that his speech and vocabulary were severely retarded. Bowden & Hopwood (1982) describe all 10 children in their series as living in conditions of 'family stress'. Abuse or scape-goating was confirmed or suspected in 7 cases. The authors describe the typical family environment, noting that there is often a chaotic household. They report that there may often be poor attachment, and poor relationships with other family members and peers. Parents are described as having rigid personalities and rigid regimes around food, only allowing food to be eaten in restricted areas. Such an authoritarian parenting style is common in our experience in families in which there is a child with the features of HSS. 'Military' style punishments involving physical endurance are often described (Skuse, unpublished data). Sexual abuse is often reported (Money, Annecillo & Lobato 1990, Stanhope at al, 1994). In sum as Green (1984) says in his review of the literature, stress plays a central part in the condition.

Some authors have attempted to place a theoretical construct on the stress described. For example Silverton, (1982) suggests that it is important to view the children in the context of the family dynamic. This area of study is crucial because it is often only within the family context that the condition is manifest. However ideas that she describes are appropriate to any other family in difficult circumstances. Money, Annecillo & Hutchinson (1985) and Money (1989) also attempt to couch the abuse or stress in terms of opponent-process learning. However again the theoretical concepts are not unique to HSS, rather they are applicable to child abuse in general.

Clearly making assessments of the degree or quality of stress experienced is fraught with difficulties. But the literature, while strongly supporting the concept that HSS manifests in chronic stress, assumes this factor is present rather than making any attempt to test whether this is invariably the case.

1.3.6.4 Mechanisms - stress as the mediator

Some studies, in assuming the mediation of stress, have attempted to theorise about how emotional stress may influence the endocrine system and retard growth. Most authors have linked the limbic system and/or the hypothalamus with HSS. For example Patton & Gardner (1962) hypothesise a causal route that might explain why some children under stress respond with a hormonal disruption, leading to growth failure. They note that pituitary hormones which control growth are influenced by the hypothalamus, which is in turn affected by the limbic cortex. The limbic cortex controls emotion and behaviour. This mechanism is hypothesised by many other authors such as Green (1986) MacCarthy & Booth (1970) Money, Annecillo & Lobato (1990) and the Powell et al team in 1967. Money, Annecillo & Lobato (1990) suggest alternatively that too much of the growth hormone inhibitor may be released (somatostatin) in conditions of stress.

It is likely that the hypothalamus is involved at some stage of the process in the manifestation of HSS. Cianfarani, Nicholl, Medbach, Charlesworth & Savage (1993) showed that dysregulation of appetite, thirst and linear growth in some cases are associated with a hypothalamic lesion. These features are central to HSS. There is also, at least in the rat population evidence that stress per se can block tissue's sensitivity to growth hormone, independent of nutritional intake (Kuhn, Evoniuk and Schanberg, 1979). This observation occurred in the presence of adequate nutrition and did not occur in malnourished pups. In the rat pup at least, a direct psychological route to hormone disturbance is documented. However rats are born at a relatively immature developmental stage in comparison to humans, so this may not be an accurate model.

Explanations 'further down stream' involving physiology rather than neurology have also been postulated. Money Annecillo & Lobato (1990) suggest that emotional disturbance may affect rate of absorption. Gardner (1972) cites a case study in which an infant was tube fed through her stomach, the mother was afraid that she would dislodge the tube and therefore inadvertently exposed her child to 'maternal deprivation'. During this time the infant's stomach secretion showed deficits in terms

of pepsin and hydrochloric acid (which helps digest food). They found that when the infant was eating or relating to an external object, the production of hydrochloric acid increased. When admitted to hospital the infant gained weight despite having the same standard dose of nutrients being administered as before via the tube.

Frank (1977) notes that there are numerous examples of 'mind-body' interactions, of which PSS (or HSS) is one. He notes that stress and the consequent rise in circulating cortisol may result in an increased susceptibility to infectious diseases and so on. That stress might have such a dramatic effect on some children, without any other environmental influences such as nutrition, or any organic influences, seems theoretically possible.

1.3.6.5 Feature resolution and separation from the stressor

The strongest argument in support of HSS being a stress responsive condition is that removal from stress leads, almost invariably, to the resolution of the core features of HSS. As we discussed above, according to some studies in which PSS and HSS and sometimes anorexic children are included in the same sample, catch-up growth is characteristic following an improved environment. We would suggest that growth hormone reversibility and consequent rapid catch-up growth is characteristic only of children with HSS. It may be that there is catch-up in PSS, but the Skuse et al (1996) article would strongly support the argument that the catch-up in HSS is mediated by growth hormone reversibility while non-HSS groups are not. The mechanism by which PSS affected children's growth rate recovers remains unclear.

Children in the Powell et al (1967a &b) study gained height and demonstrated catch-up growth *without exception* during their time in a convalescence hospital. Interestingly one sibling pair finished their catch-up growth spurt at the same time, returning to a normal growth trajectory. Another twin pair showed a similar growth rate, despite one twin having normal and the other having a retarded bone age. Behavioural recovery did not necessarily correlate with anthropometric recovery as the child who demonstrated the most impressive catch-up growth continued to show disturbed behaviour. This is a central issue. Growth and hyperphagia seem to be acutely sensitive to environmental manipulation, while the other behavioural disturbances may persist. This is important as it suggests that some features

described in these stressed children are controlled by one centre and other features that are not so responsive may be controlled via other mechanisms.

The 'treatment' for HSS, recommended in 1967 by Powell et al was removal from the stressful environment, as it is today. No medication or other interventions are required in order to demonstrate recovery. Bowden and Hopwood (1982) described a whole range of interventions including psychiatric evaluation of parents and children, psychiatric treatment of children and family, special schools and medical follow-up. Despite enormous efforts to keep children at home, 70% of their sample did not return to their biological families and those who did return, did not show 'optimal' improvement. Though HSS is a complex condition, the treatment required seems extremely simple.

Growth hormone reversibility and consequent rapid catch-up growth has been described as far as we can ascertain, in all children with the features of HSS, who had a change of environment. Most authors would agree that without catch-up (or ideally demonstration of growth hormone production reversibly on change of environment) HSS would not be the correct diagnosis. This view is held by Bowden & Hopwood (1982) who suggest that growth acceleration upon removal from a stressful home is a prerequisite to the diagnosis. They note that growth rates two to three times the normal rate may be documented. In younger children there may be an increased growth rate in terms of head circumference too.

Green, Campbell & David (1984) reviewed the literature and noted that the 'ultimate confirmation' of the condition is that children demonstrate catch-up growth and may improve in other areas when removed from the stressor. In a later publication Green et al suggest that *both* removal from the stress *and* a new positive attachment is required for recovery (Green, 1986 and 1988). However the Skuse et al (1996) data and other studies suggest that removal from the stressor is the only necessary condition.

Blizzard & Bulatovic (1992) suggest that the GH level reversibility often documented in PSS and HSS may be rapid, or may take a matter of weeks. They note one case in which reversibility took up to 12 weeks after removal from the stressor. However in the same paper they suggest that hyperphagia may not be evident in less severe cases. It may be that those children who were hyperphagic showed the rapid catch-up, and those who were not hyperphagic and had PSS caught up via a slower mechanism. Examination of the cases histories described would support this theory,

with one exception. This exceptional child reported starving himself periodically which we have not recorded to date in our HSS series - it may be that the anorexia he described delayed the catch-up growth, and this boy gained weight before height, as malnourished children do (Waterlow, 1994) which is not typical of HSS.

In further support of the rapid catch-up growth correlation with hyperphagia, Hopwood and Becker (1979) note that only 31 of their sample of 35 showed weight gain or rapid linear growth during the 2 to 4 week hospital admission. Two other children demonstrated growth acceleration but only after two months post rescue. Only two children who were removed from home failed to show any catch-up growth but these children were subsequently suspected to have permanent hypopituitarism. The variability in catch-up may have been that the sample were largely but not exclusively described as hyperphagic. We would predict that those children who failed to show catch-up or whose catch-up was delayed were not HSS.

Studies describing cases in which there was growth failure and some suspicion of anorexia do not describe the rapid catch-up growth following a change in the environment, for example Apley, Davies, Davis & Silk, (1971). Talbot et al, (1947) note that in some instances the PSS affected children grew 'at superior levels' but it is impossible to decipher whether this may be via the same mechanism as HSS without investigating growth hormone levels .

There seem to be other features that resolve in HSS affected children once they are separated from the stressor. Reinhart & Drash (1969) describe an unusual case because this affected child apparently showed spontaneous resolution of her symptoms, without an obvious improvement in environment - the only environmental change described was that she started school. Her IQ increased almost 30 points and she grew 12 cm in 9 months. It is feasible that she was grossly understimulated at home. Indeed her motor and vocabulary skills were retarded at 18 months in comparison to her brother. However it would be rather surprising that such gross neglect went unidentified. Money (1977) also supports the idea that cognitive ability as well as linear growth has enormous recovery potential in HSS. He describes improvement in IQ scores of up to 30 points. Cognitive ability is discussed further below.

1.3.6.6. Malnutrition must be excluded

The medical investigations carried out during hospital admission in the Powell et al (1967a & b) study suggest that inadequate calories were not responsible for poor growth patterns described. The catch-up growth demonstrated by all children in the convalescence home, was not the pattern of growth one might expect to see in recovery from malnutrition. HSS catch-up was far more rapid and height increased before weight. Further Powell et al note that linear growth decelerated (as opposed to weight loss) almost immediately when affected children were returned to home, despite having had an acceptable diet in hospital. The effects of malnutrition are not immediately apparent on growth, acute malnutrition results in weight loss (Waterlow et al, 1977). Woolston (1991) reiterates this noting that this condition 'is quite distinct from growth stunting secondary to malnutrition' (p37).

Other studies describing hyperphagia in their sample also note the evidence against malnutrition. Green (1986 and Green, Campbell, David, 1984) noted that after a critical review of the literature, the evidence suggests that malnutrition is not the cause of the growth retardation in PSS or HSS (according to our definition) . Blizzard (1973) clearly identifies a distinct group of children in whom there is non-organic growth failure who have low GH concentration and are not malnourished.

Mouridsen & Nielsen (1990) note there was no evidence or suspicion that the child who had shown features of HSS during foster placement was malnourished as did Money (1977). Silver and Finkelstein (1967) note that none of the children in their series appeared to have any nutritional deficits, though none were overweight despite such an apparently large food intake. This is typical in HSS. Most often children with the features of HSS have proportional weight for height but there are some exceptions. For example Wolff & Money, (1973) noted that 1/3 of their sample were actually overweight.

Blizzard & Bulatovic (1992) highlight the difference between PSS and HSS and those children who fail to grow due to inadequate diet. They document a case in which they are certain nutrition was not a factor in growth retardation but emotional stress was. Three affected children, two of whom had grown well previously when in alternative foster placements, were placed for adoption. When the children were placed in the adoptive home, all three stopped growing and were then reported to be hyperphagic. The middle child was overweight, but they note that despite having an increased intake, no excessive weight gain is usually reported in HSS cases. The

authors note that the children were apparently extremely well cared for in terms of their physical needs and well fed in the adoptive home but the placement was not emotionally nurturing. Blizzard & Bulatovic (1992) suggest that growth retarded children are either malnourished or GH deficient, and one usually excludes the other on the basis that starvation results in an increased GH response (eg Woolston, 1991).

As discussed above, samples in the literature are often heterogeneous. For example Hopwood and Becker (1979) suggest that 10% of 35 children in their series seemed, from their appearance to be under-nourished, but within their sample only 86% were hyperphagic. It is unclear whether any of the hyperphagic children appeared undernourished.

In cases where malnourishment is suspected, HSS is not the correct diagnosis, though some studies have implied that children that we suggest have PSS or HSS are actually stunted and starving. Krieger (1974) makes such a point, but on examination of the data, it is clear that the cases she is describing are not HSS (or PSS). First they are all underweight for height, second all children tested showed elevated levels of spontaneous growth hormone (though insulin intolerance tests on the same children did suggest growth hormone insufficiency) and there was evidence of malabsorption in 7 of the 10 cases. None of these factors are typical in HSS (eg Silver and Finklestein, 1967). Finally Krieger's cases' weight improved before height during admission to hospital. In other words, although Kreiger suggests in the study that her sample were similar to that described by Powell et al (1967a & b), they were in fact almost certainly children with short stature, secondary to malnutrition.

1.3.6.7. Physiology

Powell, Brasel, Raiti & Blizzard, (1967b) describe 13 HSS children in terms of their endocrinology before and after growth recovery in a convalescent home. Pituitary growth hormone was tested in 8 children. 6 cases had no or reduced response to tests (less than 5 *mμg* per millilitre). The remaining two children had normal responses (16 and 36 *mμg*).The tests were performed in one of these children three weeks after removal from home and so this normal reading may be evidence of GH level that has already recovered. The other child with normal GH levels had been growing at a normal rate for the previous two years. The authors do not comment on the timing of the all the other tests showing abnormally low readings, but data from

the Skuse et al (1996) paper show that growth hormone reversibility is evident within an average of 18 days. After the recovery period all six children with previously low growth hormone response showed recovered levels, (values ranging between 17 and 31 *mμg).* The authors conclude that emotional stress has affected the release of the pituitary hormone through the central nervous system. That postulation remains accepted today.

Mouridsen & Nielsen (1990) describe a case of HSS whose growth hormone secretion rose from insufficient levels to within the normal range during his admission to hospital. During his time in the stressful home, his growth velocity had been between 1.7 and 2.6 cm per year while rates of 5 to 7.5 cm (Woolston, 1991) are expected in normal children. Growth velocity consequently increased to above normal levels (14.3 cm per year) when placed in a nurturing home.

There are a number of studies that report variable endocrine profiles but these are the same studies that include HSS, PSS and sometimes anorexic children. Blizzard & Bulatovic (1992) note that only 53% of a series showed abnormally low GH secretion, this may be because they include children with PSS and HSS in the sample as having the same aetiology. The sample of non-hyperphagic, non-anorexic children in the Skuse et al (1996) study also had normal growth hormone levels. Similarly Hopwood and Becker (1979) showed that only 50% of the children showed an insufficient response to a GH provocation test but they included children in their sample who were not hyperphagic. Green, Campbell & David (1984) make similar conclusions but also include children with mixed aetiologies in the review.

Frasier and Rallison (1972) reported, using a case study, that children with HSS are not responsive to growth hormone, and will demonstrate catch-up only in response to environmental change. This is a view also held by Tanner (1973). Green, Deutsch & Campbell (1988) suggest that if a child does not respond to exogenous GH, this may suggest somatomedins (SM) (affected by GH) which act directly on the tissue, are deficient in terms of action or production. Such a theory fits well with Kuhn et al's (1979) data suggesting a block on tissues' GH sensitivity in maternally deprived rats pups. Children with HSS do not respond well to GH therapy but the reason why is still unclear.

Some studies report no abnormalities following numerous endocrine assessments, though GH seems to be invariably low, if it is measured. Silver and Finkelstein (1967) described numerous laboratory assessments, though no GH was measured.

This included a preliminary investigation suggesting that gastrointestinal function was normal. A similar pattern of results was reported by Reinhart & Drash, (1969) in their case study.

1.3.6.8. Behavioural features (excluding hyperphagia)

Though hyperphagia is the core behavioural feature of HSS, a number of other behavioural and emotional disturbances are described in association with the hyperphagia features.

Sleep disruption and night roaming are frequent features described by Powell et al (1967a), Money (1977) Green, Campbell & David (1984), Mouridsen & Nielsen (1990), Money, Annecillo and Hutchinson (1985), and Bowden & Hopwood (1982) also noted that many HSS children apparently required very little sleep. Skuse et al (1996) describe this feature as discriminating between HSS and non-HSS affected children. It is unlikely that the sleep disturbance per se causes short stature (Gulliford, Price, Rona and Chinn, 1989) despite the link between sleep and growth hormone production in childhood (eg Friess, Wiedemann, Steiger, and Holsboer, for review, 1995, Hayashi, Shimohira, Sasisho, Shimozawa and Iwakawa,1992).

'Aggressive' enuresis and encopresis are often described in HSS affected children, and again such behaviour discriminated between the non-HSS and HSS groups in the series described by Skuse et al (1996). This behaviour might include urination over belongings (for example Green, Schur & Lipkowitz 1959) or smearing faeces on walls (Money 1977). Money, Annecillo and Hutchinson (1985) describe two further case studies in which there was enuresis and encopresis. Blizzard & Bulatovic (1992) also note encopresis in their series.

Self-injury and pain agnosia are frequently described (for example Money, Annecillo and Hutchinson 1985 and Green, Campbell, David 1984) , though they were not discriminating variables between the PSS/anorexic and HSS series described by Skuse et al (1996). Money, Wolff & Annecillo (1972) aimed to demonstrate that children suffering from HSS show reversible pain agnosia, parallel to their growth hormone level reversibility. Many of the children in their series had been physically abused by care-givers. 63% of their sample showed self-injury according to care-givers' observations. A further 44% showed evidence of pain agnosia. The authors did not make evident the degree of overlap between those children who self harmed and those who demonstrated pain agnosia. According to reports and observation, all

the children who had previously exhibited pain insensitivity, after some time in a 'safe' environment, began to show more normal reactions to pain. 10 children relapsed into self-injury and pain insensitivity during the period they were returned to their original home environments.

It may be tempting to agree with the authors in their conclusion that reversible pain agnosia is a further core feature of HSS, as the notion of reversible physiological symptomology is cardinal to the condition. However, as the study lacks a control group it is impossible to conclude with certainty that this is a HSS specific reaction. It may be that all children who are physically abused will self-harm and exhibit reversible pain agnosia. Pain agnosia is a difficult feature to assess accurately as it relies on a reporter's interpretation of a child's behaviour. However Raymond, de Zwaan, Faris, Nugent, Ackard, Crosby & Mitchell, (1995) using an objective measure of pain sensitivity found that bulimic women had a higher pain threshold than obese or normal weight comparisons. The authors of this study concluded that poor sensitivity to pain may relate to an inability to experience satiety, in that such individuals have an abnormally functioning vagus nerve. If that were the case, one might predict that children with HSS would show characteristic pain insensitivity as they have a characteristic insatiable appetite.

Other more general behavioural disturbances are described in children with the features of HSS. Oppositional and challenging behaviour (Blizzard & Bulatovic 1992), delinquency (Green, Schur & Lipkowitz 1959), poor social relationships (Green, Campbell, David, 1984 ,Green, Deutsch & Campbell 1988), temper tantrums and apathy (Green, Deutsch & Campbell 1988) have been reported. Hyperactivity and attention deficit were also frequently recorded in the HSS group described by Skuse et al (1996).

Children with HSS do seem to show rather disturbed emotional and behavioural patterns. However, though these descriptions are important information, the behaviours cannot be interpreted as characteristic of HSS per se. As Green (1986) notes, the behavioural features described in HSS may simply reflect those seen in all children who have experienced emotional disturbance.

1.3.6.9 GH insufficiency and psychosocial disturbance

While Green makes a valid point, noting that many of the adjustment problems associated with HSS may be non-specific, at the same time there is a literature describing an association between GH insufficiency and specific pychosocial disturbances. For example Green (1986) notes that children who are depressed also have decreased GH levels. Puig-Antich et al (1984a) clarify the relationship between GH secretion and depression. They note there was an increase in GH levels secreted during 24 hours in children with depression, in comparison to 'non-depressed neurotics' and normal comparison children, which continued at least 4 months post recovery (Puig-Antich et al 1984d). However, depressed children demonstrated an insufficient GH response to *provocation tests* (Puig-Antich et al 1984b), a response also maintained four months post depressive episode (Puig-Antich et al 1984c).

Because depressed children do not show GH insufficiency over a 24 hour profile, while children with HSS do (Skuse et al, 1996), it is unlikely that there is a meaningful association between HSS and depression. Puig-Antich et al (1984a) note that there may be different mechanisms involved in GH secreted during sleep as opposed to that secreted following a provocation test. This is further supported by the fact that children with depression are not characteristically short, as children with HSS are. The authors suggest that such a pattern may be a marker for major depression, rather being associated with short stature.

A number of studies have attempted to draw together short stature in psychosocial adversity and depression or other internalising disorders as being causally linked. Ferholt, Rotnem, Genel, Leonard, Carey & Hunter (1985) described 10 short children aged between 3 and 16 years. 70% of their sample appear to have been hyperphagic. Growth hormone was not tested, but the children did show rapid catch-up growth in response to a change in the environment. Clinical data were gathered through psychiatric interviews, home observation, and psychological testing though no standardised psychiatric assessment interviews were used. All affected children were depressed according to DSM III criteria. Children appeared sad, withdrawn and were often inactive. Parent-child relationships were disturbed in every case. However they note that the 'depression' was context specific, which one would not normally expect in true clinical depression. The authors in this study suggest that growth failure is 'a neuroendocrine concomitant of a severe depressive disorder in a

person who is still growing'. They seem to suggest that the condition that they are describing is a feature of childhood depression in children who have a specific vulnerability or who have had specific early experiences. Puig-Antich et al's (1984) series of papers would not support that argument.

Boulton, Smith and Single (1992) describe 7 short children diagnosed with an attachment disorder and/or depression. The authors infer that the children are of short stature secondary to their psychosocial difficulties but this is certainly not proven. In this study, none of the seven children showed growth hormone insufficiency but they responded to growth hormone therapy. As children with HSS are growth hormone deficient (Skuse et al, 1996) and do not respond to growth hormone therapy (Frasier and Rallison, 1972), it most unlikely that these children have HSS. These children may have psychosocial disturbances but the causal link to their short stature is questionable.

Uhde (1994) describes patients who have anxiety (for example social phobia) as having a low growth hormone response to a provocation test. He suggests that without any influence of emotional abuse, children who show symptoms of anxiety may have growth hormone deficiency. In other words, he acknowledges that stress may be linked to growth hormone insufficiency as in the case of HSS but that some children who are not experiencing a stressful environment and are growth-hormone deficient, may have anxiety. Further those children who show anxiety at critical points in growth maturation may experience growth disturbance. Pine, Cohen and Brook (1996) also suggest that there may be a link between anxiety in childhood and relatively short stature post pubertal women, but not men. Height was self-reported and no measures of GH were taken in this study. However Puig-Antich et al (1984a & c) described a series of neurotic children of comparable height to the general population who showed a 24 hour GH profile and GH response to a provocation test as virtually identical to the normal comparison children (1984a). The issue of whether anxiety and GH hormone insufficiency having a functional link is still debatable.

There is little evidence to support the theory that short stature per se causes psychosocial maladjustment (Gilmour and Skuse, 1996 and Sandberg, Brook and Campos, 1994). Therefore those adjustment difficulties described above and in the HSS population should not be attributed as being a consequence of short stature.

We would suggest that these disturbances are most likely to be a reaction to environmental adversity experienced by the children with HSS.

1.3.6.10. Cognitive abiiity

In almost all cases in which cognitive ability is described, there are deficits in children with HSS features. Powell et al (1967a) report that IQ was measured in 8 cases and all of the IQ scores were below 80. Skuse et al (1996) noted that their sample of HSS cases had a mean IQ score of 76. Green, Schur & Lipkowitz (1959) describe a HSS case with an IQ of 72. Cognitive deficits are also described by Money (1977), Silver and Finkelstein (1967), Bowden & Hopwood (1982), Ferholt et al (1985) and Green, Campbell and David (1984) in their review of the literature. HSS cases with above average IQ scores have also been reported (Blizzard and Bulatovic, 1992).

Such low IQ scores may be simply due to the environmental adversity that most of the children have experienced. Money, Annecillo & Kelly (1983) note that there is evidence that abuse and neglect have a detrimental effect on cognitive ability. They described a series of children with the features of HSS. The IQ assessment was done initially while children remained in the abusive home. 23 cases were followed up and cognitively tested in a safe environment.

They tested the hypothesis that the recovery rate of IQ would be directly and positively related to the amount of time spent away from abuse. In the 23 patients who lived in abusive homes who then moved to non-abusive environments, there was an increase of 24 IQ points, a highly significant increase. Baseline IQ ranged from 36 to 101, with a mean of 66. At rescue, the mean IQ was 90 with a range of 48 to 133. A multiple linear regression equation showed that time in rescue accounted for most of the variance in IQ elevation. Baseline IQ was also a significant predictor variable. The higher baseline IQ, the greater the IQ elevation. They reported the younger patients had greater catch-up potential than older children. Goodman (1991) suggests that there is a sensitive period for intellectual development, probably to the age of 5. He suggests that environmental influences on cognitive ability during that period may be irreversible. By the same token one might argue that if deprivation occurs after that sensitive period is complete, there may be a relatively large degree of recovery potential in cognitive development. This idea is also discussed by Patton & Gardner (1975).

Money, Annecillo & Kelly (1983b) take the issue of catch-up further. By correlating height and IQ before and after rescue from an abusive environment, they show a significant relationship ($r = 0.42$, $p < 0.01$), taking into account puberty status and several changes of environment. They conclude that the mechanisms by which growth is retarded, are also involved in cognitive development in children with HSS. Without a non-HSS abused comparison group it is not possible to suggest that such IQ recovery is a feature of HSS per se.

1.3.6.11. Infant characteristics

There is no evidence in the literature of low birthweight in association with HSS. For example Mouridsen & Nielsen (1990) describe a male case, born at 3700g. Silver and Finkelstein (1967) report that all 5 children studied retrospectively had normal birth weight. However failure to thrive or infantile feeding problems are relatively common, described by Bowden and Hopwood (1982), Hopwood and Becker (1979), Silver and Finkelstein (1967) and Reinhart & Drash (1969) but it is not invariable in children with HSS features.

Motor developmental delay is also commonly described in infancy (for example Money 1977, Hopwood and Becker, 1979, Ferholt, Rotnem, Genel, Leonard, Carey & Hunter, 1985).Green, Schur & Lipkowitz (1959) describe a case history of a boy who crawled on his stomach which may be suggestive of motor milestone delay.

Care-givers of HSS affected children have described their infants as difficult in terms of temperament, but this invariably retrospective data, may be unreliable and 'tainted' in the light of the difficult relationship that care-givers and children with HSS usually had. Reinhart & Drash (1969) and Silver and Finkelstein (1967) both report that HSS affected children had been irritable as infants. Ferholt et al (1985) reported that parents recalled their children being 'demanding and unaffectionate as a neonate'.

1.3.6.12 Prevalence rate

Skuse et al (1996), on the basis of an epidemiological study, estimate that the population prevalence is around 3% of short children. Blizzard & Bulatovic (1992) note that many studies have shown a higher male to female ratio, this is supported by demographic data described by Skuse et al (1996), Powell et al (1967a), Money and Wolff (1974) and Hopwood and Becker (1979) for example. Blizzard & Bulatovic (1992) also report that though the majority of cases have been in the North American literature, all western hemisphere countries have reported cases. Different racial group are represented in affected children (eg Powell et al, 1967a).

1.3.6.13 Genetic influences ?

We argue that hyperphagia and growth hormone level recovery in response to the environment and possibly other features, distinguish HSS from any other group with non-organic short stature. This is a view suggested initially by Powell et al (1967a) and endorsed by Woolston (1991). However many children experience the type of psychosocial adversity described in association with HSS but as Skuse et al (1996) note, this condition is relatively rare. Why should some children react to psychosocial adversity in this way? Powell et al (1967b) suggest :

> 'Such factors as *personal vulnerability* and degree or length of disturbance may account for the fact that certain children suffer growth retardation whereas others, including their sibs, do not'
>
> (p 1276) .

Woolston (1991) also suggests that *either* there may be some genetic vulnerability in affected children or that there may be some specific type of psychosocial deprivation that may produce these specific endocrine dysfunctions in all children.

A wholly environmental explanation was suggested by MacCarthy (1974). He suggests that it is the continuity and length of exposure to stress that dictates the child's response. He notes that if the experience is 'intermittent' then growth might remain unaffected. In 1979 he also hypothesised that 'more continuous and less impulsive' abuse may influence growth. He suggested that there is a specific quality of the environment experienced by a child that will trigger the features of HSS in any child faced with the same circumstances.

An alternative theory as Powell et al (1967b), Woolston (1991) and Skuse et al (1996) suggest is that the child has a characteristic response to a non-specific but stressful environment. This response may be genetically mediated. Reinhart & Drash, (1969) also conclude that for an HSS affected child:

> "Perhaps the pituitary-cortical axis was her "weakest link" on a constitutional or genetic basis' (p170)

In reviewing the literature it is striking that those studies in which hyperphagia is described, also include a number of siblings within the sample. Skuse et al (1996) reported 14 children who were siblings in a series of 29 children, 4 of 13 children in the Powell et al series were siblings. Bowden & Hopwood (1982) reported 30% of their sample had affected siblings, but the inclusion criteria for siblings is not explicit and non-hyperphagic children are included in the sample. Hopwood and Becker, (1979) described three sibling pairs, plus another twin pair (it is unclear whether they were fraternal or identical) within the group of 35, but 10% of the sample were not HSS. Money, Annecillo & Kelly (1983a) describe 34 patients in which there were two sets of sibling pairs and three affected brothers. Money and Wolff (1974) report 12 cases and at least 2 were siblings. MacCarthy (1979) reports a sample in which at least some were described as hyperphagic and 2 of 15 children were sibs. Blizzard & Bulatovic (1992) describe three affected siblings, all of whom were hyperphagic. Green, Schur & Lipkowitz (1959) describe a case from a sibship of eight children, in which the index child's fraternal twin also seems to have been affected.

There are cases in which only one sibling is affected, including a pair of fraternal twins (eg Patton & Gardner, 1975). No discordant pairs of identical twins were described in our review of the literature. Interestingly we did not come across a case in which unrelated children living in the same family showed HSS features. Swanson (1994) described one hyperphagic, growth retarded child who was scape-goated in her family. Though the authors do not mention how the other children were regarded in her family, none of the unrelated adopted siblings showed such behaviour.

Following a review of the non-hyperphagic cases, only three studies reported siblings in their sample. There were 2 sibling pairs in the non-HSS group described by Skuse et al (1996). Whitten et al (1969) and Apley et al (1971) also report siblings in their non-HSS samples. It is difficult to justify why authors should systematically report siblings in the hyperphagic population and fail to do so with non-hyperphagic

children. It may be argued that there is evidence of familial aggregation in the HSS group. However, without information on the number of siblings that affected children had in total, as well as the numbers affected, it is difficult to draw firm conclusions.

1.3.7. Conclusions

The review of the HSS literature high-lights a number of points.

- First much of the literature is descriptive, without many empirical data or comparison groups.
- The description of children whom we have retrospectively identified as having HSS are a remarkably cohesive group in terms of their features. This may provide further evidence that HSS is a discrete, qualitatively distinct syndrome.
- We cannot conclude that the features of HSS are exclusive to HSS. If HSS is a syndrome that is linked to psychosocial adversity, many or perhaps all of the HSS features are normal responses to stress.
- If stress is the key to the manifestation of HSS, then why is HSS relatively rare, yet stress is relatively common? Perhaps genetic vulnerability in conditions of stress leads to HSS as some authors have speculated. Suspicions that there may be familial aggregation in HSS affected families might support that argument.

1.4 Hyperphagic or starving?

In 1.3.6.6. the importance of excluding children with signs of malnourishment from the diagnosis of HSS was discussed. However, critics such as Kreiger (1974) suggest that the hyperphagia so consistently reported is actually the behaviour of children that are starving. It is important to show that the behaviour observed in HSS, is actually hyperphagia and not a response to inadequate nutritional provision. Using children who are malnourished and those who suffer from anorexia nervosa as models, the features and correlates of HSS and starvation are compared. In the following section the correlates of hyperphagia in populations that are not affected with HSS are summarised and compared with the data on HSS that are available. One might argue that if the children with HSS resembled the starving population more than the hyperphagic population, perhaps we should agree with Kreiger (1974) and suggest that the 'hyperphagia' is really a response to starvation.

1.4.1 Starvation and malnutrition: the correlates

1.4.1.1 Physiology

Children with HSS have an insufficient growth hormone level response that recovers dramatically after removal from stressful environment (eg Skuse et al, 1996) . In contrast, Woolston (1991), among others note that growth hormone levels are elevated during chronic malnutrition and anorexia. Cho, Han and Thein (1987) note that children who are malnourished have elevated growth hormone levels which fall rapidly as refeeding continues. The children with HSS show a response precisely the opposite of this .

Xie, (1991) notes in a review of the literature that Adrenocorticotropin hormone (ACTH) increases during acute starvation in rats, though this is not a good model for chronic malnutrition. However Neufeld (1979) also described an increased responsiveness to ACTH in anorexia nervosa, in which food deprivation is clearly not acute. However she reports, in contrast, that there is a poor cortisol response to stimulation with ACTH, in chronically malnourished children. Children with HSS also have a relatively poor ACTH response (Powell et al 1967b and Green et al, 1984).

Turner & Shapiro, (1992) and Neufeld (1979) both note in their reviews that there are increased levels of cortisol described in anorexia nervosa and Woolston (1991) notes that the circadian rhythm of cortisol is disrupted in these cases. In contrast, Neufeld (1979) suggests cortisol levels are relatively normal in malnourished

children. In HSS cases cortisol levels are also low normal (Skuse, unpublished data). In terms of ACTH response and cortisol levels HSS children are similar to those with malnourishment. However such an endocrine response is also reported in healthy children, with no growth retardation who are living in conditions of emotional stress (Hart, Gunnar and Cicchetti, 1995).

Thyroid function is usually reported as being normal in children with HSS (eg Green et al, 1998, Powell et al, 1967b). Further during recovery catch-up growth, no changes in thyroid function are observed (Powell et al, 1967b). In contrast Waterlow, Tomkins and Grantham-McGregror (1992) note that the 'reduction thyroid activity (is) an adaptation to malnutrition' (p122). Hypothyriodism is also reported in anorexia (Neufeld, 1979).

1.4.1.2. Anthropometric features

Bone age in malnourished stunted children has been reported in some studies to be proportionately more retarded than their linear growth, but in others it is about equivalent to linear growth retardation (Golden, 1994). Children with HSS also have a delayed bone age (eg Reinhart and Drash, 1969 and Silver and Finkelstein, 1967) but in general this is recorded in children with non-organic short stature (eg Golden, 1994).

In conditions of malnutrition, weight loss occurs initially, followed by a decrease in height velocity (Waterlow, 1994). Children affected with HSS who are reintroduced to their stressful home, after recovery, show a reduction in linear growth before weight is affected (Powell et al, 1967b). In terms of body mass, Woolston (1991) notes that there is a loss of fat tissue in malnutrition. Waterlow et al (1977) also note that wasting is observed in children experiencing both chronic and acute malnutrition. Children with HSS are consistently reported to have a proportionate body mass index (eg Skuse et al 1996) in other words, they do not show wasting.

Further the type of catch-up growth described in 'rescued' HSS affected children and chronically malnourished children is distinct. HSS affected children show rapid catch-up in height, apparently almost immediately. While Waterlow et al (1992) have debated whether catch-up in height will occur at all if there has been malnutrition in infancy and/or childhood. The rapidity of catch-up growth in HSS exceeds that which is observed in malnourished children (Powell et al, 1967b).

1.4.1.3. Neurology and behaviour

Agarwal, Das, Agarwal, Upadhyay and Mishra (1989) found deficits in fine motor movements in children experiencing chronic malnutrition. They do not report the IQ of the children in their study. There are consistent reports of delayed development quotients in malnourished children (Waterlow et al, 1992). Though children with HSS are reported to have cognitive deficits in most cases (eg Skuse et al, 1996), specific cognitive deficits, or fine motor movement deficits have not been described.

Certain behavioural characteristics are associated with malnutrition. Woolston (1991) describes lethargy and apathy in malnourished children. Green et al (1988) describe apathy in their review of growth retarded children but included children with mixed aetiology of non-organic growth failure, not just HSS. It may be that the apathy they describe is evident in growth retarded anorexic children. Children with HSS are sometimes described as having specific psychological internalising disturbances such as depression (Ferholt et al, 1985) which may include the apathetic behaviours described by Woolston. More often, children affected with HSS show externalising behaviour. For example, Skuse et al (1996) describe overactivity as characteristic of the HSS group. Aggressive encopresis and enuresis (Money, 1977 and Skuse et al, 1996) or temper tantrums (Green et al, 1988) are certainly not behaviours that fit well with apathy and lethargy.

1.4.1.4. Metabolism and motivation to forage

Salisbury, Levine, Crow & Mitchell (1995) note that the body adapts to starvation and so the metabolic rate of starved people is lower than that of a well-fed population. Malnourished children also show reduced metabolic rate (Waterlow et al 1992).Turner & Shapiro (1992) also report that in conditions of starvation there is a reduced metabolic rate. This reduction of metabolic rate is also observed in anorexia nervosa according to Neufeld (1979). There are no studies on the metabolism of true HSS cases. Kreiger (1974) describes 'hypermetabolism' in children with malabsorption and growth failure but who do not have HSS. However, one might hypothesise that if the HSS affected children were being starved, their metabolic rate would reduce accordingly, and so might their motivation to forage for food. Those researchers with many years of experience recording and observing the behaviour of children who are chronically or acutely malnourished report that foraging behaviour is not observed (Andrew Tomkins, Professor of International

Child Health, Institute of Child Health, personal communication). It is not adaptive to continue feeling hunger when there is little food available. In contrast, our information suggests that children with HSS will go to enormous lengths to get food and that such behaviour is maintained for a number of years when living in conditions of stress (Skuse, unpublished data).

Summary:

- In terms of endocrinology, behaviour and appearance, children with HSS are distinct from those with chronic malnutrition and anorexia nervosa.
- Though cortisol levels are described as being similar in malnourished and HSS affected children (though distinct from those with anorexia nervosa), such patterns may be accounted for by different mechanisms. As so many other variables differentiate HSS and malnourished children, we might suspect that the low normal cortisol results recorded in HSS are as a result of their chronic psychosocial experiences.
- The delayed bone age described in HSS and malnourished children is not characteristic of malnourishment, but rather of short stature.

Children with HSS, according to the evidence presented above, are not starving, but do they share any correlates with other hyperphagic groups ? This literature is reviewed below.

1.4.2. Hyperphagia

1.4.2.1 The definition of hyperphagia

Hyperphagia describes an excessive appetite. Butterworth's Medical Dictionary (1978) defines hyperphagia as 'overeating, gluttony'. Describing individuals who eat more than is optimum as hyperphagic is rather vague and might mean that most of the population of industrialised countries are 'hyperphagic'. Another example of vague criteria is in Ayoob, Akaminer & Zawel's study (1994), reporting hyperphagia was identified when 'caretakers felt their (the children's) appetite was unusually large'. Hyperphagia should indicate abnormality and truly disturbed behaviour. Danford and Huber (1981) define hyperphagia as: 'an excessive appetite for food accompanied by constant searching for food, resulting in grossly excessive food intake... some individuals would eat to the point of hospitalisation for gastric pain and or vomiting' (p283). It is useful to include concrete behaviour in a definition like

Danford and Huber's. Such a definition should exclude individuals who eat large amounts but are within the normal range. The HSS diagnostic algorithm defined by Skuse et al (1996) captures similarly disturbed behaviour (see 1.3.6.2.).

This thesis does not begin to attempt to describe the mechanisms behind hyperphagia. However it is clear that there is a number of biochemical systems that are involved in appetite disturbance. This indicates that the hyperphagia described in HSS may not simply be an extreme example of comfort eating or a coping strategy for distress. In may mean that, as we have argued in terms of growth disruption, emotional stress experienced by children with HSS, may impinge on the biochemical systems involved in appetite regulation.

1.4.2.2. Systems involved in appetite regulation

A number of systems have been described in the literature as being involved in appetite regulation. In the brain for example, the hypothalamus and the medial temporal lobe are involved in eating behaviour (eg Young 1992). The neurotransmitter neuropeptide Y (NPY) has also been implicated in appetite (Morely, 1987 and Leibowitz, 1991). The hypothalamus is most receptive to NPY as it has a lot of NPY receptors. Young (1992) notes that lesions in the hypothalamus are associated with the onset of hyperphagia. The appetite increase may be due be an excess production of NPY as a result of the lesion. Clinical evidence also supports the link between NPY and appetite increase . For example, the Zucker rat which characteristically shows hyperphagia, has higher NPY levels especially in the hypothalamus in comparison to non-hyperphagic strains. Further a peptide closely resembling NPY is found to be elevated in bulimic women which would also support its involvement in appetite and satiety (Leibowitz, 1991). Castonguay (1991) reports that the adrenal glucocorticoids may also be crucial to feeding and dietary preference and Cholecystokinin (CCK) is reported to be associated with the sensation of satiety (Stacher 1986). Opioids also have a central role in feeding behaviour (Morely, 1987).

The key point here is that there may be a physiological explanation for hyperphagia observed in some cases. Excessive appetite is not invariably the result of an individual who chooses to ignore satiety because they enjoy eating or use eating as a coping strategy. There are of course many individuals who eat more than necessary, and who should not be labelled as 'hyperphagic'. We would not suggest that all people who over-eat have a physiological disruption.

Other studies have suggested that previous experience may influence the onset of hyperphagia. Lucas & Sclafani (1990) showed that particular food combinations induced hyperphagia. Rats became hyperphagic on a fat and sugar combined diet as opposed to fat alone or sugar alone . Further Ramirez (1991) suggested that genetic factors may interact with previous dietary experiences by describing the feeding behaviour of different rat strains. In other words , they suggest that genetic factors may influence susceptibility to an excessive appetite in certain conditions.

1.4.2.3. Hyperphagia, weight-gain and metabolism

Ravussin and Bogardus (1992) suggest that there may be a strong pattern of familial aggregation in metabolic rate, independent of age, sex and body weight. They suggest that obesity may for some individuals, be due to a low metabolic rate which is, they believe genetically mediated. In other words, obesity may not be due always to excess calories and inactivity.

However, in the general population excessive calorie intake is associated with increased metabolic rate. This might be expected, given the evidence presented above describing conditions of starvation. Basal metabolic rate increases in conditions of 'over-feeding'. Klien & Goran (1993) describe using the doubly-labelled water technique in young men who were eating excessively and report an increase in resting metabolic rate. In the general population, despite any increase in metabolic rate, increased calories result in an increased body mass index. There are some exceptions reported, in which hyperphagia is not associated with obesity.

Two studies, describing mutant mouse strains show such a pattern. Guastavino, Bertin & Portet (1991) described the Staggerer mouse. This strain has severe deficits in co-ordination and balance, almost certainly because they have a cerebellum one third of the normal size. In addition, the authors found that despite an increased food intake (of a factor of 1.5) the mutant mice had a body weight half that of the controls. Cummings, Brandon, Planas, Motamed, Idzerda and McKnight (1996) also recently described RIIß null mice who are healthy and of normal size and length but who do not become obese despite eating an excessive diet.

Equivalent evidence in the human population of hyperphagia without weight gain is scarce. Though Morely (1987) observes that methadone addicts are underweight,

despite eating above average amounts of calories. In general it seems that chronic peripheral administration of neuropeptides will lead to weight loss.

1.4.2.4 Hyperphagia in chiidren

Aside from the HSS literature, hyperphagia is very rarely mentioned in the human literature, unless it is in relation to organic disease such a diabetes or recognised conditions such as Prader-Willi syndrome. We found only two studies that focused on hyperphagia in children, but whom the authors report are not affected with HSS or any other recognised condition. These studies are examined in detail, though they are not particularly well designed studies, because they seem to describe hyperphagia in 'normal' children.

First Demb (1991) identified a group of fostered children who were hyperphagic but whom she believes do not have the condition that Powell et al (1967a & b) described. The second study describes hyperphagia in children who are not described as having HSS. Ayoob, Akaminer & Zawel (1994) report a group of 13 fostered children who ate excessively but were not obese. These children are very similar to those described in the HSS population in terms of showing hyperphagia but having a normal body mass index. Are they really cases of HSS?

Demb (1991) suggests that hyperphagia may be a marker for psychosocial disturbance in children, rather than a marker for HSS as we might suggest. Certainly short stature is not characteristic of the group she describes as a whole (see the table below). If the children were HSS cases, then one might expect that the point at which hyperphagia is reported might be the time at which growth retardation would *begin* because Skuse et al (1996) note that hyperphagia disappears when growth recovers. From examination of the growth charts, it seems that there are only three children who have growth data available 6 months or more following the onset of reported hyperphagia. Two of these children showed growth along or below the 5th centile (and were the shortest in the group), another was showing a height velocity decreasing from the 25th height centile. More prospective data are required to confirm whether we might suspect that these are really HSS cases. Another point of interest is that at least 4 of the children who were described by foster parents to be hyperphagic were administered types of medication which can increase the appetite (Tu, Hartridge and Izawa, 1992).

Table 1.4.2.1 The anthropometric data from Demb's study (1991):

child ID	*height at first report of hyperphagia (centile)*	*weight at first report of hyperphagia (centile)*	*height profile*	*weight profile*	*medication*
1	?	?	increases	increases	?
2	90th	90th	stable	increases	no
3	25th	75th	stable	stable	yes
4	5th	10th	stable	variable	?
5	75th	90th	stable	stable	yes
6	-5th	-5th	stable	stable	yes
7	+25th	+25th	stable	stable	no
8	25th	-25th	stable	decreases	no
9	+25th	-90th	increases	stable	yes
10	5th	5th	decreases	increases	?

Ayoob, Akaminer & Zawel, (1994) also described hyperphagic children in foster care who were not all of short stature as their heights ranged from the 5th to the 90th centile. Data for individual children are not given, but it may be, as with Demb's data, the children who have demonstrated hyperphagia for the longest period of time are shortest in stature. Given the data, we can only speculate about what proportion of these children may be HSS. It may be that none of the children have the condition. Clearly it is important to establish the cases in which hyperphagia is documented but HSS has been excluded. It is interesting, too that both Demb's and Ayoob et al 's studies described foster children who we might guess are living in, or have experienced conditions of stress.

1.4.2.6. Proposed mechanisms of hyperphagia in chiidren

Both Demb (1991) and Ayoob et al (1994) comment that many of the natural mothers of the hyperphagic children had alcohol or drug problems and imply that this may explain the children's behaviour in part. However, Ayoob et al (1994) had no comparison group and there were no data available on the comparison group's mothers in Demb's study. Maternal substance use is a common pattern in all foster children (Halfon, Mendonca and Berkowitz, 1995). Ayoob et al (1994) also suggest that 'emotional stresses' might also explain the hyperphagia described in their sample, but do not elaborate further.

1.4.2.5. The cognitive and behavioural correlates of hyperphagia

Cognitive ability:

Hyperphagia and learning difficulties seem closely associated as described in the children with HSS (eg Skuse et al 1996). Ayoob, Akaminer & Zawel, (1994) also reported that cognitive functioning was poor in general for the hyperphagic children though one child was of 'average intelligence'. Demb (1991) reported that 9 of 10 hyperphagic children that she described required special education.

Taking another perspective, Danford and Huber (1981) found that 14% of a learning disabled population were hyperphagic and they suggested that the more severe learning disabled population had the most disturbed appetite. They do not mention whether any of the sample had Prader-Willi syndrome (PWS), a genetic condition described fully in 1.6, in which those affected show learning difficulties and hyperphagia. However the tendency for obesity and excessive eating is recorded in other learning disabled populations that exclude PWS (eg Bell and Bhate, 1992). Holland, Treasure, Coskeran and Dallow (1995) note that though eating disorders and excessive appetites are recorded in the learning disabled population, the eating pattern described in PWS is more severe. There may some blurring between 'overeating' and appetite disturbance captured in the label hyperphagia. Where hyperphagia is described, it is likely that the individual will have low IQ, but hyperphagia is not characteristic of the learning disabled population.

Disturbed sleep:

Danford and Huber (1981) described that disrupted sleep patterns were significantly correlated with hyperphagia. This suggests that for some individuals, an insult to the hypothalamus, may result in disruption of sleep and appetite (Fix,1995). Other studies have also described an association between sleep and appetite disturbance in adults (Oswald and Adam, 1986 and Stunkard, Grace and Wolff, 1955). Sleep disturbance is also described as being characteristic of the HSS population (eg Skuse et al, 1996).

Psychosocial disturbance:

Drawing only on the Demb (1991) and Ayoob et al (1994) studies, hyperphagic children are described as invariably having disturbed psychosocial adjustment. Ayoob et al (1994) report profiles of aggression and destruction. Demb also noted conduct disorder problems in 40% of her sample. Ayoob et al (1994) described the

hyperphagic children as 'active' but the children did not score in the abnormal range for hyperactivity in the questionnaire used, though 4 of 10 children in Demb's study were identified as having attention deficit with hyperactivity. The remainder of Demb's sample had atypical pervasive developmental disorder or infantile autism and Ayoob et al (1994) notes that social withdrawal was described in their population. Clearly both samples were disturbed and in many respects the difficulties resemble the psychosocial problems described in the HSS children. These children have been fostered, presumably due to the psychosocial problems described in their biological families. Demb (1991) describes behavioural profiles for a comparison group of non-hyperphagic fostered children, showing a significantly higher incidence of pervasive developmental disorder, but the other diagnoses are not compared. As discussed in section 1.3.6.8, it may be that the disturbances in the these children are those expected in many children experiencing psychosocial adversity.

1.4.3. The starving, hyperphagic and HSS populations compared

There are a number of points to be made in summary:

- There are more physiological data available in the literature concerning starvation than there are concerning hyperphagia, making direct comparisons difficult.
- Many of the behavioural and anthropometric comparisons between the hyperphagic and HSS populations are using Demb and Ayoob's data. As discussed above, if some of these children are in fact affected with HSS, this may be a comparison of one HSS affected group with another.
- In terms of IQ deficits, sleep pattern and evidence from non-obese hyperphagic mice, the HSS children's data fit with hyperphagic populations more closely than those from malnourished or starving populations. On that basis then it seems that the HSS affected children are truly hyperphagic and not as Kreiger (1974) suggested, starving.
- A systematic comparison between HSS and another hyperphagic population would be an important addition to the debate about HSS and hyperphagia.

1.5 The correlates of stress

1.5.1. Aims and problems

'Stress seems to apply equally to a form of stimulus.. a force requiring adaptation(strain)... a mental state (distress) and a form of bodily response..' (p1) (Rutter, 1983). Defining the limits of stress is difficult and has been debated for many hundreds of years, but recognising a condition or experience as stressful is rather easier. The environmental conditions described in the HSS literature (see section 1.3.6.3) are clearly stressful.

This section aims to review the literature describing the physiological and behavioural correlates of children (though adult or animal data are used where no other data are available) who do not have any organic disease and living in conditions of chronic stress. HSS has been described in the literature as a condition that is often associated with stress, so it is important to review the literature concerning chronic stress in other populations. The literature describing stress is vast, and for that reason review articles have been included. The aim in the section below is to introduce the correlates associated with chronic stress rather than an exhaustive review of the topic or its definition.

Because of the physiological dimension described in HSS it is important to examine the physiological as well as the emotional and behavioural consequences of stress. Rutter (1983) notes that physiological stress reactions are largely documented by exposure to experimental physical stressors such as heat, while the psychosocial adjustment consequences of stress are described largely on the basis of observation of individuals who have experienced emotional distress. In other words, the physiologists largely use a different group of stressors in their literature than the social scientists but this should not confound our aim.

There are a number of difficulties in the 'stress literature' which we must consider. Much of the literature describes acute stress. First, the physiological effect of acute stress is almost invariably different from that in chronic stress, as the body habituates to constant threat (eg Sapolsky, 1992). Second, animal models are used in many studies describing the physiological aspects of stress but animals models cannot inform accurately on the behavioural consequences of stress. Third, stress

induction in laboratory conditions does not necessarily generalise to real-life stressors, as demonstrated by data presented by Shapiro, Jamner and Goldstein (1993). Fourth, suggesting that animals experience emotional distress in the same manner as humans do, is problematic.

Below we review the literature on three topics. First data on Post Traumatic Stress Disorder are summarised, a diagnosis which may be informative for HSS to some degree. Second the physiological effects of chronic stress on the body and third the associations between chronic stress and psychosocial adjustment are described.

1.5.2 Post Traumatic Stress Disorder (PTSD)

1.5.2.1 PTSD and HSS

PTSD is a cluster of symptoms, described further below, observed in a proportion of adults and children following their exposure to a traumatic event. It is a condition described in ICD-10 (World Health Organisation, 1992) and DSM-IV (American Psychiatric Association, 1987). The literature on PTSD is not strictly relevant to HSS, as it concerns the effects of an adverse experience which has occurred previously while HSS seems to be associated with concurrent stress. In other words, in PTSD the traumatic event has passed. Children who demonstrate the symptoms of HSS, do so *during* their chronic experiences (eg Powell et al 1967a & b) and characteristically recover after the stressor is discontinued. However one might argue that because the experience is continuing to affect children in PTSD that they are in fact experiencing chronic stress. Although the PTSD affected child is no longer exposed to the aversive stimuli, the experience continues to influence the child's psychosocial adjustment. Yehuda, Resnick, Kahana and Giller (1993) present data that suggest there may be non-significant trends of physiological differences in those with PTSD as opposed to those who were unaffected, 45 years after the event. Indeed Yule (1994) notes in his review of the literature that the physiological effects of an acute trauma may persist long-term, even after the psychological symptoms of PTSD have resolved. The other differentiating factor between HSS and PTSD is that PTSD is most often associated with one acute event, such as a shipping disaster (Yule, 1992). Though chronic experiences are also described with reference to PTSD as some authors described the effect of sexual and physical abuse in terms of PTSD symptoms (Yule 1994). This type of stressor occurs frequently in the descriptions of HSS affected children.

In sum, PTSD is a human condition that occurs in the context of stress and emotional distress and for that reason it is important to be aware of the symptoms and issues of the condition. The PTSD literature as Yule (1994) notes is potentially informative for the study of other stressors. Those people exposed to a disaster for example, are not selected, volunteered, of one particular socio-economic group or subject to referral bias. These biases are often described in the literature reporting the effects of other stressors such as family discord or abuse.

1.5.2.2. The features of PTSD:

Yule (1994) summarises some of the symptoms associated with PTSD. He reports sleep disturbances, insecure attachment, irritability, concentration problems and relatively poor school performance, guilt about having survived a disaster that others hadn't, and intrusive thoughts about the incident. Children affected with PTSD may also experience the sensation that the traumatic experience is reoccurring (Trad, 1989) and they may experience somatic complaints such as head-aches (Vogel and Vernberg, 1993). Children as young as four years old may be severely affected by traumatic events (Yule, 1994).

Physiology:

Charney, Areil, Deutsch, Krystal, Southwick and Davis (1993) review the psychophysiology of PTSD. They suggest that many of the symptoms of PTSD can be explained by an increased noreadrenic function as well as endogenous opiate withdrawal and hypothalamic-pituitary-adrenal (HPA) axis activity following a stressor. This is described further below.

Cognitive correlates:

The cognitive correlates of PTSD are described by Shalev and Rogel-Fuchs (1993) who note that there may be a long-term change in the sensitivity to certain internal imagery and auditory stimuli. Such hypervigilence is also supported by Thrasher, Dalgleish and Yule (1994) using emotionally laden words in the Stroop effect, though they infer that this cognitive style may be a precursor rather than an consequence of PTSD.

1.5.2.3. Individual differences

Evidence from PTSD shows that the more severe the stressor experience, the more severe the subsequent reaction and the longer the symptoms of PTSD will remain (Yule 1994). Such a linear relationship might lead us to suspect that most children have a similar perception of an event as the children's perception might be inferred from their reaction. Further Yule (1994) suggests that deliberate acts of violence may have more severe consequences than natural disasters for example. This suggests that for most of the population, trauma experienced due to deliberate events are perceived as more stressful than those perceived to be accidental. While this may be true as a general population characteristic, there are also individual differences in the way that some children perceive and judge the same event (Yule 1994). The powerful effect of different perceptions in the population is also emphasised by Sapolsky (1992). Individual differences in the perception of the same stressor is a theme running through-out the stress literature.

Many other independent factors may influence the effect of a stressor on a particular child. For example Yule (1994) notes that family factors may act as a moderating variable in the expression of PTSD. Vogel and Vernberg (1993) also note the importance of family and community factors. It is clear that there are a number of internal variables (for example, perception) and external variables (for example, family support) specific to a child that influence the manifestation of PTSD. The theory that the relationship between trauma and PTSD is *indirect* is supported by the fact that not all those children who experience the same event will develop symptoms of PTSD (Yule, 1992). Yehuda, Resnick, Kahana and Giller (1993) suggest that the previous conceptualisation of PTSD as a normative response to trauma should be questioned precisely because not all traumatised individuals develop PTSD. Thrasher, Dalgleish and Yule (1994) provide evidence that individuals with chronic PTSD symptomology 5 years post disaster show disaster specific information processing biases. They suggest that such an information processing style might be a *predictive* marker of more severe PTSD. In other words this effect may not be as a result of the PTSD but may have a causative role in maintaining or inducing the symptoms.

1.5.1.4 Developmental issues

Another factor which might be regarded as an additional individual difference is developmental stage. The developmental effect of exposure to trauma is not clear. It seems likely that there should be such an effect simply because of the dramatic cognitive changes that occur through-out childhood, bearing in mind the role that cognition seems to play in the development of PTSD symptoms. Yule (1994) notes that clinically, pre-school children have a different reaction following trauma than older children (as opposed to more or less severe). There may indeed be a qualitative distinction in different age groups, but any quantitative differences that may exist on the developmental continuum are not yet established. There are a number of methodological difficulties that may confound the establishment of such developmental patterns. Parents and teachers may not report internalising symptoms accurately (Hodges, Gorden and Lennon, 1989) but as Vogel and Vernberg (1993) discuss, recording younger children's symptoms will inevitably involve parent or teacher report to a greater degree than older children .

1.5.2.5. Summary

The literature on PTSD demonstrates two points that are pertinent to the exploration of HSS.

- First that the effects of stress can be disabling and can be associated with distinct patterns of cognition and physiology.
- Second, though in general stress has detrimental effects on a child, there may be individual differences in the precise manifestation of the effect. A number of environmental factors such as family or community support may be crucial in influencing the PTSD stress reaction. Other factors may be influential, and though Yule (1994) notes that as yet there is no evidence to suggest that PTSD is mediated or moderated by genetic factors, such an explanation may prove to play a role to some degree.

1.5.3 The physiological correlates of stress

In this section we concentrate on the pituitary adrenal stress response as this is the system which has been researched most extensively (Yehuda et al, 1993). Endocrinology is also a central feature of HSS. There are other systems involved in the body's stress response such as the sympathetic nervous system, which are not described.

Sapolsky (1992) reviews the literature on the physiology of stress. The data provided below are applicable to a whole range of chronic stressful experiences. Though there is some evidence that specific physical or disease stressors may elicit a specific stress response, as a general rule many different stressors cause the same physiological reaction. There seems to be no evidence suggesting that different psychological stressors such as neglect as opposed to sexual abuse for example will produce specific physiological responses. However Rutter (1983) notes that emotional and behavioural responses, as opposed to physiological reactions, may be event specific. This is discussed further below.

The stress response can be measured by hormones, mainly glucocorticoids and adrenaline (epinephrine). There are 'stress reaction' pathways involving the hypothalamus and the pituitary, all of which involve brain activity resulting in chemical changes in the body which ultimately affect tissue and organs, including the brain (Hellhammer and Wade, 1993).

1.5.3.1 Acute stress

The chain of events following exposure to an acute stressor is as follows: corticotrophin releasing hormone is released from the hypothalamus. Corticotrophin releasing (CRF) hormone stimulates the pituitary to release adrenocorticotropic hormone (ACTH). ACTH stimulates the adrenal and glucocorticoid hormones are then released (the most dominant form is cortisol). There is a feed-back loop that maintains the appropriate HPA hormone level in the body (Yehuda et al, 1993). Other hormones are released during acute stress such as ß-endorphin, vasopressin glucagon, and growth hormone.

In acute stress the key is energy mobilisation - this is the best solution to a short term challenge, but in chronic stress, this is not adaptive. The body can not sustain the acute reaction persistently, and therefore in conditions of chronic stress, the response is different to that described above for acute stress. For example if levels

of CRF are continually elevated, the number of CRF receptors will decrease and so the ACTH response to CRF will be desensitised - keeping the system in homeostasis (Hellhammer and Wade, 1993). Rutter (1983) notes that, broadly speaking, the body's response to chronic stress is adaptation. Using the feed-back systems, the body regulates itself even in perpetual challenge (Hellhammer and Wade, 1993). The result is that the endocrine picture in chronically stressed individuals is not dramatically different from non-stressed individuals on many variables. The consequences of chronic stress are detrimental as Sapolsky (1992) notes ' with sustained stress, the stress response can eventually be as damaging as the stressor' (p296).

1.5.3.2 Chronic stress: cortisol

In chronic stress cortisol levels are within the normal range or diminished, the response to CRF is blunted, and the number of glucocorticoid receptors decreases (Hellhammer and Wade,1993). There are some exceptions in which elevated cortisol levels are reported in chronic stress (Davidson, Weiss, O'Keefe & Baum, 1990). In general though, the finding that, due to adaptation, the body does not sustain elevated cortisol levels in chronic stress is a relatively consistent finding in animal and human data. For example Kant, Bauman, Anderson, & Mougey, (1992) showed that after three days of intermittent stress (a foot shock), stressed rats showed significantly greater levels of plasma cortisol than controls, but by the 14th day all rats in stressed and non-stressed conditions showed cortisol levels that were comparable to baseline levels. In other words, the stressed rats showed habituation to the stressor between the 3rd and 14th day of stress. This finding is also described in primates experiencing restraint stress. Wantanabe, Gould and McEwan (1992) note that after 4 days of stress, monkeys showed an habituated cortisol response to the stressor though in the previous days the monkeys had shown an elevated cortisol stress response.

A similar picture is reported in chronically stressed humans, showing a resting cortisol level within normal ranges and a blunted response to a repeated stressor. Yehuda et al (1993) report that such attenuation in chronic stress does not apply if the stressor is novel. In other words, one might theorise that if an unfortunate animal (or human) was exposed to a series of stressors, each different from the last, the cortisol stress response would be equally intense with each new stressor. Hart, Gunnar and Cicchetti (1995) describe cortisol levels in physically abused

children in comparison to socio-economically matched comparison children. They found that there was no significant difference between the groups in baseline cortisol, but that the abused (or chronically stressed) children had a blunted response to the acute stressors that they encountered during their school day. Such HPA activity attenuation is also reported in those individuals with PTSD, rather than an overactive or over-sensitive reaction as previously thought (Yehuda et al, 1993).

The mechanism of this attenuated response may be a sensitised feed-back system, so that the response to a stressor is less intense and does not last as long in chronically stressed individuals as compared to non-stressed individuals. Yehuda et al (1993) support this theory by showing that individuals with PTSD showed an exaggerated suppression in response to the dexamethasone test, as compared to normal comparisons and individuals who had experienced trauma but were not exhibiting PTSD.

There is a potential confounding factor in describing cortisol levels in individuals with PTSD as affected individuals may also be depressed. Depression is associated with elevated cortisol levels (Bauer, Priebe, Graf, Kurten & Baumgartner, 1994) . Individuals who had recently fled from East to West Germany (n= 84) who had developed psychiatric disorder within 6 weeks of their arrival in the west were compared to 20 healthy controls. Bauer et al (1994) found that there was a non-significant trend for the traumatised cases to show a lower afternoon level of serum cortisol than comparisons , though still within the normal range. They found that those cases who had major depression had significantly higher cortisol concentration than the other individuals who had a variety of different psychiatric disorders.

1.5.3.3. Chronic stress: appetite

When the body is fed or starved for a long period of time, the HPA system is stimulated (Dallman, Akana, Bradbury, Strack, Hanson and Scribner ,1994). Dallman et al (1994) describe the effect of stress on appetite in acute conditions but suggest that in chronic conditions of stress there may be a propensity to continue eating with increased insulin levels which facilitates energy or fat storage, resulting in obesity. In other words, long-term stress may stimulate food seeking in rats.

1.5.3.4 Chronic stress: growth hormone and growth

Sapolsky (1992) notes that in chronic stress, the growth of rat pups can be inhibited. Humans also show decreased levels of GH, but the precise mechanism by which that happens is not known.

As discussed above (see 1.3) the relationship between stress and growth in children is complex. Sapolsky (1992) notes that the poor growth often seen in children in a war zone, for example, may be due to the poor nutrition they receive. Children in such circumstances may also be anorexic *because* they feel stressed.

There are children who fail to grow despite having adequate nutrition and normal GH levels. These children have excess levels of glucocorticoids. Children with Cushing disease have perpetually high levels of glucocorticoids as do children who receive glucocorticoid therapy. It seems likely that excess glucocorticoids may inhibit the growth promoter somatomedin (Unterman and Phillips, 1985). However as we have described, conditions of chronic stress do not result in elevated glucocorticoid levels in the general population. Further physiological data from children with HSS suggest that cortisol levels are not elevated (Skuse, unpublished data) suggesting this is not the mechanism for their growth failure.

1.5.3.5. Individual differences in the physiological stress response

As discussed with reference to PTSD, there are a number of factors which may influence the physiological stress response in an individual. First previous experience, second genetic factors and third an individual's perception of the challenges that a particular stressor presents.

Previous experience:

Stress reactivity can be influenced by early separation from the mother in rat pups. The experience may decrease or increase stress reactivity. For example, Weiner and Levine(1983) described stress immunisation in which rats handled preweaning did not respond so severely to stressors encountered later in life. But other evidence suggests that early stressors may increase future stress reactivity. De Kloet (1996) suggests that rat pups, when separated from their mothers for just one day, had enlarged adrenal glands and their reaction to stress in adulthood resulted in a higher level of adrenal hormone and a prolonged stress reaction. Kagan (1983) notes that maternal stresses in the 4th to 6th week of conception may influence the

development of the automatic nervous system, on the basis of rat studies. Kagan suggests that there may be a similar mechanism in humans though Hellhammer and Wade (1993) note that there is no evidence yet for such a long-lasting effect in humans. Rat studies should be interpreted with caution as rats are born at a developmentally immature stage as compared to human infants - there may be systematic differences on that basis alone. However there is evidence from non-human primates that stress during pregnancy may result in an altered immune system during infancy, though it is not clear how long such an effect response might last since data were not available more than 6 months postnatally (Coe, 1993).

Genetic influences:

Genetic factors are also influential in stress reactivity. Sapolsky (1992) suggests that genetics may mediate some individual differences, at least on the basis of rat studies. Some rat strains are more susceptible to stressors than others. It might be argued therefore, that genetics may play a part in the individual differences demonstrated in the human stress response, and more specifically the response demonstrated in HSS. Ciaranello (1983) also highlights the importance of genetic mediation of stress responses in the neurochemical stress response system.

There is some evidence from research involving humans that genetics play a role in baseline cortisol levels, but the evidence is weak in supporting a genetic influence on stress reactivity . For genetically identical twins, baseline cortisol correlations are $r = 0.87$, CRF stimulated values are $r = 0.88$, physical stressor values are $r = 0.7$ and psychological stressor values are $r = 0.85$, while non-identical twins show correlations of 0.43,0.46,0.86,0.69 respectively (Keirschbaum, Wust and Hellhammer, 1992). However, sympathetic nervous system stress response measurements may show genetic influences, as much of the variation in stress response measured by heart beat can be explained by racial group (Kagan, 1983).

Individual perception

It might be argued that both previous experience and genetics may influence an individual's appraisal of a stressor. The subjective experience of a stressor is difficult to measure systematically (Hellhammer & Wade, 1993) but it does affect stress reactivity. Hellhammer and Wade (1993) also add another complication - the same stressor, such as a mental arithmetic exercise, experienced by the same person may be perceived as stressful in one context but not in another.

Other social context factors may influence individual perception and therefore stress reactions. Position in the social hierarchy has been demonstrated to influence stress response both in baboon social structures and human ones (Hellhammer & Wade, 1993). Sex differences described in relation to stress response may simply be social artefacts. For example men show a cortisol reaction double that of women in reaction to a physical stressor, but that may be because men perceived the threat of a physical stressor as greater than women because of social expectations that they should be physically competent (Hellhammer and Wade, 1993).

Sapolsky (1992) summarises the features of an experience that may make it stressful: loss of control, unpredictability, and a lack of means to express frustration. There is evidence that these factors do objectively influence stress. For example rats exposed to uncontrollable shock initially show an elevated cortisol response in comparison to those exposed to controllable shock (Kant et al 1992). However, one might argue that an individual's perception of these same factors may be as powerful in dictating a stress reaction as the objective evidence available to that individual.

1.5.4 The psychosocial correlates of chronic stress

1.5.4.1 Stress in HSS

As Rutter (1983) commented, many of the behavioural and emotional correlates of chronic stress are documented on the basis of psychosocial as opposed to physical stressors. This may in fact be fortuitous for our purposes as some studies imply that different stressors such as losing a relationship as opposed to being threatened may have differential consequences in terms of psychosocial adjustment (Rutter, 1983) but probably not physiological reactions (see above). Therefore, in terms of understanding and predicting the psychosocial adjustment that one might expect in children with HSS, it is important that the literature reviewed is describing the same type of life experiences that are associated with HSS. According to previous literature, the chronic stressors associated with HSS revolve around child maltreatment in the family, with sexual (Money et al, 1990, Stanhope et al, 1994), emotional (Money, 1977, Bowden and Hopwood, 1982, Powell et al, 1967a) and physical abuse (Money, Wolff and Annecillo, 1972) all commonly reported.

1.5.4.2 An indirect iink between stress and reactions

Rutter (1985b) suggests that stressors and their negative consequences on emotional and behavioural adjustment have been described for over two hundred years. There is increasing evidence that a stressful environment or psychosocial adversity does not lead directly to emotional and behavioural difficulties, but that many factors may intervene in that process (Rutter, 1985b). While the effects of psychosocial adversity and maladjustment may be indirect, there is undoubtedly a strong association between the two factors. This is best illustrated with an example. Jensen, Richters, Ussery, Bloedau and Davis (1991) reviewed the life events of a sample of children with adjustment problems in comparison to a socio-economic status matched community sample. They found that the referred sample had experienced more stressful life events such as parental divorces. Further analysis showed that such life events may be due to parental functioning which may in turn lead directly or indirectly to the life event stressors. In other words, parental psychopathology rather than the life events themselves seemed to account for the children's disturbance. Some of the other risk and mediating variables are summarised below but the main aim of this review is to document the correlates of chronic stress rather than understand the mechanism by which stress effects adjustment. Understanding the mechanism is important, but it is beyond the scope of this thesis.

1.5.4.3. Risk variables

There are a number of stressors that have been reported to be associated with abuse and child maltreatment in general. Young single mothers who have been abused themselves are at risk of abusing their own children (Healy, Kennedy and Sinclair, 1991). Social isolation and poor social support are also linked to abuse in families (Kolko ,1992 and Rosenthal, 1988). Other risk variables include maternal stress or psychopathology, financial problems and father's unemployment (Kolko, 1992 and Rosenthal, 1988).

Sherrod, O'Connor, Vietze and Altemeier (1984) describe another feature associated with abuse. They suggest that abused children may have more anatomical abnormalities and illnesses than non-abused children, pre-dating reported abuse. This indicates that illness in the family adds extra stresses which may then be related to abuse, rather than illness leading directly to abuse. Many ill children were not abused even if their siblings had been abused. Further, ill health

was a common feature in infancy rather than later childhood, while the abuse continued into childhood.

Some risk variables are associated with specific types of abuse. Though there is clearly much overlap between these factors and those associated for general child maltreatment. Wolfner and Gelles (1993) report that physical abuse occurs more frequently in low income families in which there are four or more young, particularly male children aged 3 to 6 years old, in which the father is unemployed and in which care-takers had used drugs as opposed to alcohol at least once. The link between physical abuse, large families, young children and low income is also made by Jones and McCurdy (1992) but they note that low socio-economic status is not characteristic of families in which there is sexual abuse. However substance abuse or parental psychopathology is frequently reported in sexually abusing parents Beitchman et al (1991). Emotional abuse is described as being associated with the back-ground factors for general child maltreatment described above, in addition to poor coping strategies in the care-giver (Hickox and Furnell, 1989).

Other studies have suggested that features in the child who is abused may interact with parental features resulting in a poor parent-child relationship. Bugental and Shennum (1984) report that they 'trained' children to be difficult by spending a proportionately small amount of time on task, showing a delayed response, looking away from the adult and being verbally unresponsive. Adults with low perceived control over their care-giving ability reacted negatively with the difficult children (but positively with 'easy' children), using an unpleasant tone of voice and facial expression. In other words, care-giver attributions in conjunction with a difficult child may lead to poor interactions and perhaps ultimately abusive ones. However other authors suggest that child centred factors are not contributory to maltreatment. Dodge, Bates and Petit (1990) suggest in a prospective study that a difficult temperament was not a predictor of physical abuse.

1.5.4.4. Internallsing correlates of stress

Depression and depressive symptoms, particularly suicidal ideation are frequently reported in children who have experienced stress. For example Jensen, Richters, Ussery, Bloedau and Davis (1991) in their review note that 'life stressors' in children's lives are correlated with depression. Depression and depressive symptoms are also described in relation to abuse and neglect specifically as compared to 'normal' children and non-abused clinical groups (eg Skuse and

Bentovim, 1994, Beitchman et al 1991, Watkins and Bentovim, 1992 and Sirles, Smith and Kusama, 1989, Rimsza, Berg and Locke, 1988). Some authors suggest that depression is more commonly reported in sexual, as opposed to other forms of abuse, but this may be due to the fact that there are more girls reported to have been sexually abused and girls are more likely to show internalising reactions to life events than boys (Beitchman et al 1991). Depressive features are also described in children who have not been sexually abused. Dodge et al (1990) noted that internalising difficulties are more frequently reported in physically abused children than controls, and girls in particular showed withdrawal and isolation, which they suggest may be precursors to depression. While others have noted that depressive symptoms may be more common in adolescents rather than younger children (Skuse and Bentovim, 1994).

Other studies have described a number of different internalising features in association with child maltreatment. In their review of the literature Watkins and Bentovim (1992) described low self esteem, fearfulness and emotional upset in sexually abused children. Kolko, Moser and Weldy (1988) suggest that withdrawal, fear or mistrust are reported significantly more frequently in sexually abused as compared with physically abused children. Similarly Livingston (1987) suggests that depression is more common in sexually abused children than children who have been physically abused. Sirles, Smith and Kusama (1989) describe the psychiatric status of 225 children who had experienced sexual abuse within their family. They identified 'adjustment disorder' in over 20% of their sample. A further 0.5% reported an anxiety disorder.

General internalising adjustment problems are also described frequently in the literature, for example Watkins and Bentovim (1992) report sexually abused children as more likely than comparisons to score in the clinical range for internalising problems. Children whose father was violent towards their mother show significantly more internalising problems than a children from a non-violent home (Holden and Richie, 1991).

1.5.4.5. Externalising correlates of stress

Children living in stressful circumstances are described as 'acting out' (Jensen et al 1991). More specifically children who have been abused are also described as having externalising adjustment problems.

Aggressive behaviour is reported in association with non-abusive stressors such as heat and over-crowding (Lewis, 1992). Aggression is also described in children who have experienced inconsistent and impulsive parenting (Skuse and Bentovim, 1994 for review). Children who are exposed to marital violence but are not abused themselves show aggression particularly towards their mother (Holden and Richie, 1991).

Aggression is also reported in those children who have experienced abuse, though Kolko (1992) suggests that anti-social and aggressive behaviour is more frequently reported in children who have been physically abused than those who have experienced other types of abuse, as does Livingston (1987). Children who have been physically abused often have an aggressive style in general, for example Haskett and Kistner (1991) observed physically abused children to be more violent towards their peers.

Dodge, Bates and Petit (1990) also note that there is a link between aggressive behaviour in children who have experienced physical abuse and suggest a mechanism for that process. Using a longitudinal design the authors describe aggression towards peers as more common in physically harmed children than non-abused children, taking socio-economic status factors into account. They suggest that physically abused children have a characteristic cognitive style as they tend to attribute hostile intent to others and show poorer social problem solving skills.

Other externalising problems such as hyperactivity and conduct disorder are reported in association with abuse (Sirles et al 1989) as are acting out and stealing (Watkins and Bentovim, 1992). Externalising difficulties are reported from various sources, for example, Hart et al (1995) describe greater acting out or externalising problems in young physically abused children as compared to non-abused according to teacher ratings. Other studies suggest that children who have witnessed violence between their parents show comparable externalising problems (though increased tendency to violence) to children from non-violent homes (Holden and Richie, 1991).

It seems that, largely, different types of abuse have comparable effects on adjustment but Beitchman et al (1991) note that sexualised acting out is a specific reaction to sexual abuse in childhood, certainly in comparison to physically abused children (Kolko, Moser and Weldy, 1988). Freidrich (1993) noted that sexualised behaviour in sexually abused children is a robust finding, evident from numerous types of assessment and different sources of information.

1.5.4.6. Peer relationships

Difficult interpersonal relationships are reported in children whose parents have a violent relationship rather than children who are themselves physically abused (Holden and Richie, 1991). In addition, many children who have been abused themselves have poor peer relationships (eg Skuse and Bentovim, 1994). Poor peer relationships have serious long-term repercussions, predicting and perhaps causing psychopathology and other adjustment problems (Williams and Gilmour, 1994). A number of studies have used direct peer report to describe the peer relationships of abused children. Physically abused children have poorer peer relationships than socio-economic status (SES) matched non-abused children. Further there is evidence that sociometric status may not be significantly associated with other family functioning variables (Salzinger, Feldman and Hammer, 1993). Haskett and Kistner (1991) also described low sociometric status in physically abused pre-school children as compared to SES and IQ matched control children.

With poor peer relationships, there are a number of associated social interaction difficulties. For example, peers describe physically abused children more negatively than non-abused children - for example low co-operation (Salzinger et al, 1993). Such negative descriptions from peers may be because peers do not like the abused children, however Haskett and Kistner (1991) independently observed more 'negative' behaviour in the class-room in physically abused children as compared to matched controls.

Physically abused children also display difficulties in terms of their dyadic friendships, which are distinct from the relationship with a peer group. Abused children rated some children as friends but those same children reported disliking the abused children (Salzinger, Feldman and Hammer, 1993). This lack of reciprocity has also been observed in the class-room (Haskett and Kistner, 1991). It seems likely that the difficulties that abused children have with social relationships

are caused or at least exacerbated by the information processing and social problem solving skill deficits described by Dodge et al (1990) above.

1.5.4.7. Somatic complaints

Rimsza, Berg and Locke (1988) describe that a variety of somatic complaints in sexually abused girls are reported significantly more frequently than a non-abused control group. They describe muscle tension, gastrointestinal problems both of which may be non-specific stress responses as well as features that may be specific to sexual abuse such as genitourinary symptoms, though Livingston (1987) suggests that somatic complaints may be peculiar to children who have been sexually abused. Rimsza et al (1988) also note that just under 70% of their sexually abused sample showed emotional or somatic symptoms and Sirles et al (1989) describe somatisation in their sample of sexually abused children.

1.5.4.8 Cognitive ability

Rutter (1985c) describes environmental influences on cognitive development in children. He notes that compared to the effect on socio-emotional adjustment which is described above, cognitive ability appears to be relatively unscathed following care-taker disruption, parental psychopathology and family discord, all of which might be regarded as chronic stressors for a child. Yule and Rutter, in 1968, noted that there was an association between anti-social disorders and poor attainment. Children with internalising and externalising disorders scored about one half of a standard deviation score in IQ below comparison children without any adjustment difficulties. The groups were matched for family but not 'social' characteristics. It may be that the children described in the 1968 Isle of Wight study showed maladjustment and poor attainment because of a specific factor, but it may be that the 'third factor' was socio-economic deprivation - causing adversity.

Rutter (1985c) points out that many of the studies showing cognitive deficits in children in psychosocial adversity are confounded by the fact that the 'stressed' group are often socio-economically deprived to a greater degree than comparison groups. Skuse and Bentovim (1994) review the literature and note that cognitive deficits in abused children are well reported, for example Sirles et al (1989) describe 3% of their sexually abused sample as having learning difficulties, but like Rutter they suggest that socio-economic disadvantage correlates are not controlled. Kolko (1992) also suggests that the numerous cognitive deficits associated with child

maltreatment such as memory problems, general cognitive ability, reading and perceptual motor skills may be due to social disadvantage. However there are exceptions to this confounder. For example, Friedrich, Einbender and Luecke (1983) describe overall cognitive ability, memory and verbal skills as being significantly lower in pre-school physically abused children as compared to non-abused children matched on a number of socio-economic variables.

Where poor performance in cognitive tests or poor attainment at school are reported in 'stressed' or abused children, other associated factors have been suggested as possible explanations: poor nutrition, under-stimulation, neurological damage following physical abuse or simply low motivation during testing (Skuse and Bentovim, 1994). In other words, the link between poor cognitive performance and child maltreatment is indirect, but commonly reported.

Taking a different perspective, some authors have suggested that poor cognitive ability is a risk factor for abuse. Beitchman et al (1991) reviewed the literature and concluded that attainment and performance on cognitive ability tests at school may indeed be poor in sexually abused children in comparison to peers and other psychiatric comparison groups but note that poor cognitive skills may pre-date the abuse. This suggests that low cognitive ability may in fact be a risk variable for sexual abuse. However, cognitive deficits are not described invariably in children who have been sexually abused as Rimsza, Berg and Locke (1988) note that there are no significant differences in 'school problems' (including school performance) when sexually abused girls are compared with a control group .

There is a third angle on cognitive ability and adversity. It might be hypothesised that if a child with a relatively high IQ were abused for example, then such a child would be less likely to show maladjustment following that experience than a child with low cognitive ability. In sum its seems that children with above average IQ scores are less likely to show psychosocial maladjustment (Rutter, 1983). The reason for this observation is not understood but it is possible that children with above average cognitive ability are protected to some degree from stressors. It might be argued therefore that the children described above are those who lack the protective factor provided by higher than average cognitive ability, rather a group of children who show cognitive deficits as a result of psychosocial adversity.

In conditions of extreme social deprivation, there is stronger evidence that the cognitive deficits described are a direct effect of the child's circumstances, rather

than the indirect effects listed above. Rutter (1985c) reports that severe environmental insults involving isolation or sensory deprivation are associated with severe cognitive ability deficits. In 1972 Rutter made the point that a lack of stimulation encapsulated in severe social isolation or neglect, is associated with developmental delay. It is wrong to suggest that developmental delay is a stress response, rather in this case it is because the child has not been stimulated. In other words, this is the nature of the direct effect. Rutter goes on to note that verbal attainment may well be the dimension of attainment most affected by lack of stimulation. Once a child is moved to an environment which is cognitively stimulating, some cognitive catch-up is characteristic. This pattern of cognitive skill improvement seems to occur in severe cases of abuse where a child is isolated and cut-off from stimulation, not 'just' physical, emotional or sexual abuse. Cognitive ability does reflect the quality of the environment to some degree. In addition to the environmental influences, a genetic effect on cognitive ability is well established (eg Rutter, 1985c).

1.5.4.9. Appetite

In addition to the literature reviewed in 1.5.3.3 there are other studies reporting the effect of stress on appetite. Using an animal model, Restrepo and Armario (1987) noted that prepubertal rats did not have an altered food intake or body weight during a chronic intermittent restraint stressor lasting 32 days. However, Kolko et al (1988) report that poor appetite occurs significantly more often in sexually abused children than physically abused and non-abused clinical referred in-patient children.

Morely (1987) in his review, notes that stress may increase eating or chewing due to the release in endogenous opioids following data in mouse studies. Though he notes in human studies emotional stress increases eating in about half the population and decreases it in the other half. This might reflect differential patterns of adaptation. The 'normal' appetitive reaction to chronic emotional stress is not yet well established in humans.

1.5.4.10. Other correlates

There are a number of other factors which are commonly described in abused or traumatised children. Difficulties in sleep and sleep disorders are reported in abused children (eg Watkins and Bentovim, 1992) as is self harming and self-injurious behaviour (Kolko, 1992).

Poor attachment may be a precursor to adjustment problems in the future. Rutter (1985b) reviewed the literature concerning the loss of an attachment figure and described this particular stressor as being linked to depression in later years, though the link between the two events may well be indirect. Poor attachment may also be a symptom of child maltreatment as described by Kolko (1992) and Skuse and Bentovim (1994) in their review, with the same detrimental long-term effects.

Adversity or maltreatment may influence a child's life perspective. For example Ney, Moore, McPhee and Trought (1986) described children who had been verbally abused as having a pessimistic view of the future. 46% of their sample who had been verbally, sexually or emotionally abused, described feeling unwanted by their family. Further the authors described children who were abused as feeling that they were responsible for the abuse. Such internalising, negative attributions could be regarded as symptomatic or precursors to depressive symptomology.

Numerous reports of general psychosocial adjustment problems are reported in the literature. It is clear the likelihood of developing some type of adjustment problem following abuse or trauma is high. For example, Sirles et al (1989) report that in all 40% of their sexually abused sample had a clinical condition of some description, while 70% in Rimsza et al's study (1988) had either an emotional or a somatic complaint. Even when SES is taken into account children in abusive families are more disturbed according to parents and teachers than those in non-abusive families (Salzinger, Feldman and Hammer, 1993). Exposure to violence, as opposed to being on the receiving end of physical assault also results in general adjustment problems (Holden and Richie, 1991).

1.5.4.11. Individual differences in psychosocial stress responses

As with the PTSD and the physiological literature there are some factors which influence the type of psychosocial response to adversity. Developmental stage, genetic factors and previous experience which may result in resilience or

vulnerability and individual perceptions are key factors that may account for the variation in adjustment responses

Developmental stage:

Rutter (1983) suggests that there are some developmental stages at which children are clearly particularly vulnerable to specific events. For example, between the ages of 6 months and 4 years, hospital admission may have more serious repercussions for children, than admission before or after that period. Before 6 months the child does not have the cognitive capacity to form an attachment which would be broken during hospital admission. Children over the age of four years have the cognitive ability to understand why such a separation is required. However, most other stresses and their consequences cannot be so neatly compartmentalised in terms of a developmental perspective, as Yule (1994) notes with reference to the vulnerability of children in conditions of trauma or disaster. Yule (1994) does suggest that younger children may be protected to some degree because they do not have the cognitive capacity to be fully aware of their circumstances. Data provided by Sirles, Smith and Kusama (1989) may support Yule's view as they described adolescent victims of sexual abuse as being more likely to be diagnosed with a psychiatric condition than sexually abused prepubertal children.

However, age related trends are confused by the adjustment problems described in adolescents in the general population. Rutter, Graham, Chadwick and Yule (1976) note that when taking into account internalising problems which are under-reported by parents and teachers, it seems likely that there may be a small but significant rise in psychosocial symptoms from 10 years to 14 years. The type of disturbances reported were largely similar across middle childhood and adolescence but depression and school refusal became more prevalent in adolescence as opposed to middle childhood. Therefore, apparent age trends showing poorer adjustment following adversity in older children and adolescents might be due to the general population trends.

Beitchman et al (1991) note that the confusion in age trends in the literature may also be due to different time delays between abuse being discovered and assessment, and the length of abuse. Older children are more likely to have been abused for a longer duration, and are more likely to have experienced force. This suggests that the abusive event may be systematically different in older children,

rather than older children having a systematically different reaction to the stressor. The issue is not yet resolved.

Genetics:

Rutter (1983) reports that genetic factors may influence both the degree of reactivity to any given stressor and also the form that the reaction might take. In other words, one person's reaction to chronic stress may be depression, another may become alcoholic. Temperament, also genetically determined at least in part, may also shape stress responses, both the degree and the type of that response. Plomin and Rowe (1979) demonstrated that there may be heritability in terms of the reaction to strangers in infancy - a classic stressor.

Previous experience:

Previous experience may influence a child's reaction to future stressors - such experience may result in vulnerability or reliance. This is not the forum in which to review such factors, but simply to note that such mediators may exist (see Rutter, 1985b). Many of the risk factors described in section 1.5.4.3 may also be viewed as factors that increase a child's vulnerability to stress.

Individual perception:

There is less emphasis on an individual's differential perception of maltreatment or abuse in the literature - perhaps there is a threshold of adversity, after which all individuals will experience stress and an adverse reaction. However, one might argue, that in the same way not all children exposed to trauma develop PTSD, not all children who have been maltreated develop adjustment problems. For example Rimsza et al (1988) suggest that 70% of their sample showed somatic and emotional complaints. Should we then infer that the remaining 30% were unaffected?

There does seem to be a linear relationship between the severity of the abuse or stress and the maladjustment that follows the abuse (Skuse and Bentovim, 1994) suggesting, as with PTSD, that most children regard the same features of an event as stressful. In other words, there is a consensus view about the aspects of an experience that make it aversive. Sirles, Smith and Kusama (1989), note that sexual abuse from a parental figure was more likely to be associated with a psychiatric diagnosis than if abuse came from other family members. Further, the more frequent, longer in duration, or if the child experienced other types of abuse in

conjunction with sexual abuse (for example physical assault), the more likely the victim would have a psychiatric condition. Other studies have provided a slightly different message. Rimsza, Berg and Locke (1988) note there is a linear relationship between the duration and the number of emotional, behavioural and somatic symptoms in children who have been sexually abused but no relationship between the number of symptoms and the type of abuse.

1.5.5 Summary

A number of factors emerge from this review of the literature.

- First individual differences caused by environmental or genetic factors are influential factors in stress responses in the 'normal' population.
- Second though the mechanisms may be complex and the relationships indirect, there is a consistent relationship between psychosocial adversity, (abuse specifically) and a number of emotional, behavioural and cognitive features.
- There are clearly many parallels between the HSS group, who seem to be characteristically stressed, and those 'normal' individuals who are not, as far as we know, growth retarded but who have been exposed to stress. In terms of physiology, a low normal cortisol level and a relatively poor ACTH response is common to both groups. Sleep disruption, self harming, externalising behaviour problems, poor social relationships, attachment problems, cognitive ability deficits, difficult temperament, depressive symptoms and other internalising problems are associated with the children affected with HSS and the children who are experiencing psychosocial adversity.
- In many ways children with HSS are typical of children in adversity. At the same time there are a number of features central to HSS that are not described in stressed children. Growth failure and appetite disturbance are not reported in stressed children in the general population, but this may simply be because researchers did not address these issues specifically. A comparison of children in stress with HSS is clearly warranted.

1.6 Prader-Willi Syndrome

1.6.1 A genetic definition

Prader-Willi syndrome (PWS) was first described in 1956 by Prader, Labhart and Willi. Identification of the genetic anomaly associated with the condition came 25 years later. Ledbetter, Riccardi, Airhart, Stribel, Keenen and Crawford (1981) discovered that the anomaly associated with PWS was on the long arm of chromosome 15. Initial diagnosis relied on cytogenetics which can be rather imprecise. Approximately 40% of those individuals who appeared, clinically to have PWS, had apparently normal chromosomes. More exact molecular techniques such as methylation status tests (eg Dittrich, Robinson, Knoblauch, Buiting, Schmidt, Gillessen-Kaesbach, Horsthemke, 1992) and DNA CA repeat markers (described by Mutirangura, Greenberg, Butler, Malcolm, Nicholls, Chakravarti and Ledbetter 1993), have shown that all PWS de novo cases have some anomaly at 15q11-13 (The American Society of Human Genetics, 1996). All the deleted alleles in PWS are paternal in origin (Butler and Palmer, 1983), which indicates that the PWS critical region is imprinted. In other words, a paternal contribution at the PWS critical region is essential for normal development. Two maternal alleles (uniparental disomy) results in PWS in the same way that a deleted paternal allele and an intact maternal allele does. An American Society of Human Genetics publication (1996) notes that 70% of individuals with PWS have a deletion at 15q 11-13, a further 28% have uniparental disomy and the final 2% have an imprinting mutation.

Gillessen-Kaesbach et al (1995) suggest that the different molecular mechanisms associated with PWS have little effect on the phenotype. They note that those individuals with a deletion are more likely to show hypopigmentation (relatively fair colouring) and low birthweight, while those without a deletion, most commonly uni-parental disomy, have significantly older mothers.

Though the region associated with PWS has been identified, the gene or genes responsible for it have not yet been mapped. The SNRPN gene was a strong candidate for PWS (Lalande, 1994), as it is functionally imprinted and in the critical PWS region, but as yet no PWS affected individuals have shown a deletion of SNRPN alone.

1.6.1.1 Sibling Recurrence rates

Though most anomalies in PWS are sporadic, there are cases of sibling recurrence. Pembrey, Clayton-Smith, Webb and Malcolm (1992) suggest that taking into account the different mechanisms causing PWS, the sibling recurrence rate risk is 1% or less. While Donlon (1992) notes that all familial cases to date have normal cytogenetic results and suggests that if both parents are cytogenetically normal then the chance of reoccurrence is low, but that the recurrence is not established where there is a familial translocation. Lubinsky, Zellweger, Greenswag, Larson, Hansmann and Ledbetter (1987) describe four children affected with PWS in one sibship with, as Donlon (1992) had noted, apparently normal chromosomes. It may be that molecular tests rather than cytogenetic tests would have provided more detailed information about the nature of the anomaly in these siblings. Orstavik et al (1992) described an affected sibling pair, in which there was no evidence of any anomaly at the PWS region using cytogenetic or DNA markers. Sibling recurrence has more recently been linked to an imprinting mutation which would be detectable by only methylation status studies (Reis et al,1994).

It is unclear precisely how the deletion on chromosome 15 results in the PWS phenotype but as many of the characteristic features are related to the hypothalamus, Cassidy (1992) suggests that there is a hypothalamic dysfunction in PWS affected individuals. Further Cassidy (1992) notes that individuals with a lesion in the hypothalamus show similar features to those in PWS as described below. In support of this theory Swaab (1991) described distinctive features in the hypothalamus of individuals affected with PWS following post-mortem studies.

1.6.1.2. Prevalence rate

There is debate about the true prevalence of the condition. Donaldson, Chu, Cooke, Wilson, Greene and Stephenson (1994) suggest that previous estimates of 1 in 10,000 births are too high, due to over-diagnosis of PWS. The same group suggest that unless a molecular investigation can confirm the diagnosis, caution should be exercised in making the diagnosis (Chu, Cooke, Stephenson, Tolmie, Clarke, Parry-Jones, Connor and Donaldson, 1994). There are other estimates of incidence rates, for example Butler (1990) suggests an incidence rate of 1 in 25,000, and Robinson et al suggest 1 in 15,000 following a Norwegian study. Using molecular techniques in combination with the clinical diagnostic criteria developed by Holm et al (1992), a

more accurate prevalence rate may now emerge. Holm's diagnostic criteria describes major and minor features of the syndrome in relation to a comparison group. Many PWS descriptive studies lack such comparison groups.

The condition has a distinct natural history (eg Cassidy, 1992, Butler, 1990) with rather contrasting features in infancy as compared to those features described in child and adulthood. These are described separately below.

1.6.2 Infant characteristics

Poor muscle tone (hypotonia) is evident in almost 100% of infants with PWS. Between 90% and 100% of affected infants have feeding problems and consequent poor weight gain (Cassidy, 1992, Butler, 1990). The feeding problems are caused by hypotonia. Affected infants have poor sucking and gagging reflexes. Hypotonia and poor weight gain are major diagnostic criteria of PWS (Holm et al 1992). Ehara, Ohno and Takeshita (1993) described a series of 11 PWS cases followed longitudinally from birth. They noted that birth weight was below the population mean in all cases and often over 1.5 sds below the mean. Tube feeding was necessary for 100% of their sample. Poor weight gain continued to the age of 6 months old, then slowed further in some cases between the ages of 10 and 18 months. After 18 months weight gain increased dramatically, signalling the end of the infancy stage.

Motor milestones are delayed in PWS, and usually reached in double the average time described in the general population (Cassidy, 1992), such delays occur almost invariably (Butler, 1990). Holm et al (1992) suggest that poor foetal activity, a weak cry and lethargy are all supportive findings of PWS, though more common in atypical cases.

1.6.3 Features described in children and adults with PWS

1.6.3.1 Hyperphagia

Perhaps the most distinctive feature of PWS is hyperphagia. 80-90% of children with PWS become hyperphagic, which often results in obesity (Cassidy, 1992). Though in our experience obesity is certainly not inevitable. Hyperphagia usually begins before the child is 6 years old according to Holm et al (1993) and occurs at an average age of 2 years old (Butler 1990). Other estimates of the average onset

are higher (eg Holland et al, 1993). Curfs (1992) suggests that with age the appetite disturbance becomes 'more noticeable'. This may simply be due the increasing levels of independence allowed as the child gets older, allowing greater access to food, rather than an increase in food craving.

Many studies report hyperphagia on the basis of anecdotal reports but Zipf and Berntson (1987) describe an observational study of children who had PWS in comparison to obese children. They report that children with PWS ate significantly more calories during an hour observation, though at a similar rate as obese children. Holland, Treasure, Coskeran, Dallow, Milton and Hillhouse (1993) also describe an observational study in which the amount eaten and the metabolic changes that followed are described in a group of adults with PWS and age matched non-obese controls. They note too that the PWS group did indeed eat significantly greater amounts of calories than the comparisons. In this study the authors asked the participants how hungry they felt, rather than inferring this from their behaviour as Zipf and Berntson (1987) did with children in their study. The adults with PWS reported that they felt more hungry before eating and during the hour long experiment than the comparison group. At the end of the hour both groups reported comparable satiety - indicating that individuals with PWS can feel full too, if only after a greater number of calories than the comparison group. However, after having reported being full, 40 minutes later the adults with PWS began to report hunger again.

Holland, Treasure, Coskeran and Dallow (1995) note that care-takers reports of PWS subjects' eating behaviour at home predicted behaviour that was observed and recorded by researchers over a period of an hour. Those who ate least during observation were reported to require only verbal restraint to discourage eating at home - though the body mass index (BMI) of the 'verbal restraint' group was rather higher than the group mean. Clearly individuals with PWS report hunger. Their hyperphagia seems to be an attempt to maintain a sensation of satiety and in response to hunger.

A number of studies have attempted to identify the physiological reasons behind the reported hunger. Zipf and Berntson (1987) examined the effect of the opioid inhibitor Naloxone on children affected with PWS, testing the hypothesis that the

opioid system might the key to the increased hunger apparent in PWS. Their results showed administration of the drug had no significant effect on the amount of calories eaten. They caution that other aspects of the opioid system may be responsible for the appetite disturbance observed in PWS. Tu, Hartridge and Izawa (1992) also suggest that appetite-suppressant drugs are not effective in controlling hyperphagia in PWS, though other studies have reported success in hospital admitted case studies (eg Dech and Budow,1991 and Benjamin and Buot-Smith,1993).

Holland, Treasure, Coskeran, Dallow, Milton and Hillhouse (1993) took blood samples from PWS and non-obese comparison groups during an hour long session in which there was free access to food. Metabolic changes recorded following eating suggest that there is no impairment of in the release of cholecystokinin (CCK) in individuals with PWS . CCK has been implicated in satiation following eating (Morley,1987). Holland et al (1993) note that other anomalies in the CCK system remain possible explanations for the lack of satiety response in people with PWS. Further they note that blood glucose rises in direct relation to the amount of food eaten in the PWS affected individuals, as one would expect in the general population. However the PWS group had blood glucose above the expected range which might indicate a characteristic insensitive satiation response in the PWS population. There is evidence that children with PWS have a blunted pancreatic polypeptide response (which may be involved in appetite regulation), even in comparison to obese children (Zipf, O'Dorisio, Cataland and Dixon, 1983). However the reason why people affected with PWS seem to experience hunger to a greater degree than the general population remains unclear.

1.6.3.2. Obesity

Probably as a consequence of excessive eating, obesity is often associated with PWS. There seems to be a characteristic body fat distribution with weight often distributed around the trunk (Cassidy, 1992). Though there is evidence that this group eat excessively, affected individuals do maintain preferences for different kinds of food. Taylor and Caldwell (1985) report that sweet foods are often preferred and would be chosen over larger amounts of less preferred food. High preference foods have been used successfully as positive reinforcement, to encourage activity in one sample of adults with PWS (Caldwell, Taylor and Bloom,

1986). Some authors suggest that hyperphagia in PWS has a environmental component. Taylor (1992) cautions that hyperphagia is not invariable in PWS and that the eating behaviour demonstrated by individuals with PWS might be similar to any other individual who is living in an environment of continuous food restriction. Obesity in PWS can become so severe that there may be physical (and life-threatening) complications, in addition to a poor quality of life (Holland et al, 1995). Maintaining a reasonably low body mass index is the key to successful management of PWS.

1.6.3.3 Links between behaviour disturbance and hyperphagia

Other behavioural disturbances are reported to appear around the onset of hyperphagia. For example, Cassidy (1992) suggests that skin picking is observed in 70-80% of cases. Greenswag (1987) reported that of 232 adults with PWS, 78% showed skin picking. Clarke, Waters and Corbett (1989) also reported that approximately 85% of the adult PWS population showed skin picking 'frequently'. Temper tantrums are also frequently reported (Cassidy, 1992, Butler, 1990) in addition to descriptions of belligerence and stubbornness (Greenswag 1987). Taylor (1992) also notes that aggressive behaviour has been reported in cases of PWS, as is poor judgement relative to measured IQ level (Sulzbacher et al 1981).

Many of these descriptions are limited because they lack an appropriate comparison group which would help identify which behaviours are characteristic of PWS. Further there are methodological limitations in many studies. For example Greenswag (1987) asked care-takers to rate the severity of certain behaviours in subjects with PWS, rather than providing concrete descriptions of behaviour that care-takers could endorse. Greenswag's method is problematic because different care-takers may judge appetite disturbance, for example, using their own particular criteria of what constitutes a severe or a mild problem.

Butler (1990) suggests that some behavioural difficulties may start as a consequence of the food restriction imposed upon the individual with PWS that will inevitably follow when hyperphagia begins. Whitman and Greenswag (1992) note that individuals with lower BMIs are more likely to have behavioural problems, adding evidence to the theory that behavioural problems may be associated with the demands of weight reduction and management in PWS. However in an earlier

publication, Greenswag (1987) notes that adults with PWS who have a relatively high BMI were rated by care-takers as having behavioural disturbance more frequently than the adults who had PWS and a relatively low BMI, on at least some dimensions. Other studies have reported no relationship between BMI and behavioural disturbance in adults (Clarke, Waters, Corbett, 1990).

1.6.3.4. Activity level

Children and adults with PWS have a reputation in the literature of being rather inactive, probably exacerbated by co-ordination problems resulting from hypotonia. Problems with obesity following excessive eating will also be increased by inactivity. Nardella, Sulzbacher and Worthington-Roberts (1983) suggest that the range of activity levels during a summer camp stay measured by pedometers and actometers, is greater in children with PWS than non-obese controls. They do not report the group means of activity levels which makes it rather difficult to conclude whether inactivity, at a summer camp at least, is characteristic of PWS or not. However it is clear that weight loss was positively correlated with activity levels, supporting the theory that inactivity contributes to obesity in PWS. Davies, Joughin, Livingstone and Barnes (1992) confirm that children with PWS are characteristically inactive. They used doubly labelled isotopes in the home environment over 10 to 14 days, and as compared to a non-obese comparison group, children with PWS showed a significantly lower total energy expenditure. They were relatively inactive in comparison to non-obese children, after taking into account age, sex and weight.

1.6.2.5. Cognitive and neurological features

97% of PWS affected individuals have an have an IQ below 70 (Butler, 1990), with the average IQ reported, for example, as 62 (Dykens, Hodapp, Walsh and Nash, 1992b). There are a number of descriptions suggesting a profile of relative cognitive strengths and weaknesses in PWS. For example visual processing skills are reported, in some studies, as being relatively strong. Skill in completing jigsaw puzzles was described by Holm et al (1992) in 6 % of typical PWS cases, but none of a comparison group. Curfs, Wiegers, Sommers, Borghgraef and Fryns (1991) note that their sample of PWS affected individuals showed a relatively high score on block design in an IQ test, a sub-scale which taps into visual organisation skills. However such a finding is not consistently reported. Gabel, Tarter, Gavaler, Golden, Hegedus and Maier (1986) reported that block design scores ranked relatively low

against other sub-scale scores. The same group administered a wide neuropsychological battery to a group of children with PWS and a comparison group with an IQ in the normal range. They found that, in addition, to lower global ability, children with PWS had deficits in attention, perceptual-motor integration and motor control relative to children with normal IQ - all of which exacerbate the PWS group's poorer performance on IQ testing. There was evidence that stimuli involving the oral modality was more difficult for the PWS group than material in the visual modality - though this may be due either to middle ear disease or a neurological deficit. The finding fits well with other reports that visual processing is a relative strength for the PWS affected population. Dykens et al (1992b) suggest that sequential processing was relatively weak while attainment and achievement were relatively strong in people affected with PWS, aged 13 to 46 years old. However other sources are more sceptical of such characteristic profiles. Taylor (1992) believes when individuals with PWS are compared to learning disabled comparison, the only characteristic aspect to their cognitive profile is relative skill in visual organisation.

Waters, Clarke and Corbett (1990) noted that though just under half of children with PWS attend a mainstream primary school, by secondary school age the proportion in main-stream education has dropped to 11.5%. They note that such a shift in placement was not likely to be due to a developmental decline in IQ. This conclusion is supported by Dykens, Hodapp, Walsh and Nash (1992b) who reported that in contrast to Down's syndrome, there was no evidence of IQ decline in PWS in their cross sectional or longitudinal data. However, the longest time between test one and test two was 9 years, the mean testing interval was only 3 years 3 months.

Other studies have examined the relationship between cognitive ability and behaviour. Dykens and Cassidy (1995) found no relationship between IQ and maladaptive behaviour, but did find a significant positive relationship between low BMI and adaptive behaviour. Dykens, Hodapp, Walsh and Nash (1992) reported a significant positive correlation between adaptive behaviour and IQ.

Sleep architecture studies have indicated that there may be a neurological basis to the reports of disruptive sleeping patterns in PWS. Helbing-Zwanenburg, Kamphuisen and Mourtazaev (1993) using objective measures, note that 95% of

their sample of PWS affected children and adults had excessive day-time sleepiness, as compared with 10% in the adult normal comparison group. During night sleep, the PWS group showed a significantly lower proportion of rapid eye movement (REM) and slow wave sleep than the comparisons but there was no evidence of the sleep apnea syndrome in any PWS cases tested. Excessive day-time sleepiness is also commonly reported (Clarke et al, 1990) which may be exacerbated by sleep interruption during the night.

1.6.3.6. Speech difficulties

PWS is also associated with speech difficulties and such problems are apparent in around 80-90% of cases (Cassidy, 1992). Kleppe, Katayama, Shipley and Foushee (1990) assessed children and adolescents with PWS and found articulation problems, difficulties in terms of expressive and receptive language, including difficulties with syntax. The battery of tests in this study was extensive, with most instruments having standardised norms for the general population, but a IQ matched control group may have been more informative in order to identify PWS specific speech problems.

1.6.3.7. Psychosocial adjustment

There are a number of studies exploring the general psychosocial adjustment of children and adolescents with PWS. Curfs, Verhulst, Fryns (1991b), used the Child Behavioural Check-list (Achenbach and Edelbrook, 1983) , and confirmed that against the general population, the PWS group had significantly more adjustment problems. Without an appropriate comparison group, we are unable to say whether such a profile is characteristic of people with PWS or the learning disabled population as a whole.

Greenswag (1987) suggests that behavioural maladjustment increases with age in adults with PWS, but does so on the basis of comparing her data with previous reports in children and adolescents. Curfs (1992) also suggests, but does not cite evidence, that in adolescence there is an increased risk of psychopathology in PWS. It is worth considering that such an increase in psychopathology is apparent in the general population to some extent (Rutter et al 1976). Dykens and Cassidy (1995) document an increase in symptoms in younger children with PWS as compared to those aged 8 to 12 years, but they used a behavioural scale which

does not seem to be standardised for different ages within that range, as the Achenbach Child Behaviour Checklist (CBCL) scales are, for example (Achenbach, 1991). The scale that they had used was standardised for children with learning difficulties. The same study assessed a group of adolescents and adults who had PWS, but they do not provide any evidence that symptoms increase in adolescence as compared to adulthood. The children's group was not compared directly with the adolescent and adult group, therefore the theory that PWS affected individuals have increased symptomology in adolescence cannot be explored.

Dykens, Hodapp, Walsh and Nash (1992) suggest that adolescents with PWS show significantly greater *differences* between externalising and internalising problems than adults with PWS, with externalising problems being more frequent. There was no evidence that the *average combined number* of problems increased with age across this age range. The CBCL scales used in the study are standardised for children up to the age of 16, therefore it is rather difficult to conclude with certainty whether there are any age related changes using the standardised scores. Comparison across age groups using raw score may have been more meaningful.

1.6.3.8 Physiological features

In addition to the evidence that individuals with PWS are inactive, other studies have indicated that there may further complications in maintaining a low BMI. Butler (1990) suggested that the resting metabolic rate in PWS was relatively low. But Davies et al (1992) report that children with PWS had a comparable basal metabolic rate, predicted from weight and height, to a population sample.

There is debate whether PWS is associated with growth hormone deficiency or whether the blunted GH responses recorded are due to obesity. Angulo, Castro-Magana,Uy and Rosenfeld (1992) examined the 24 hour growth hormone profile in obese and non-obese children aged 1 to 15 years who had PWS. They reported abnormally low levels in all the children regardless of BMI. Further, using provocation tests and a 12 hour secretion study, Costeff, Holm, Ruvalcaba and Shaver (1990) noted an insufficient growth hormone level peak in all 6 children, 5 of whom were not obese (in comparison to published ranges of children in the general population). They caution that growth hormone studies can be inconsistent and need replication in order to validate them. Ritzen, Per Bolme and Hall (1992) also

note that the unusually high body fat ratio described in PWS, even without obesity, may influence GH levels. Urinary growth hormone profiles over 24 hours for 22 children and adults with PWS showed low GH levels (Blichfeldt, Main, Ritzen, Skakkekaek, 1992), though this group were mostly obese, the lowest readings were in the youngest children who were the least obese. 66% of the children showed GH levels below the 25th centile of the levels reported in the general population.

Other studies are more cautious in their support of the GH insufficiency theory. Ritzen, Per Bolme and Hall (1992) describe 8 young people with PWS aged 7 to 19 years and a group of control children who were obese. They report a non-significant trend for the PWS group to have lower GH levels than obese comparisons when measured an hour before and after falling asleep, before and after 20 minutes of exercise and in response to a provocation test. The PWS group's GH level was *significantly* lower than the obese group an hour after falling asleep. However 70% of the group showed an insufficient response to GH provocation tests, as compared to the expected level in the general population.

There is also evidence to suggest that there may be other endocrine disturbances associated with PWS. Garty, Shuper, Mimouni, Varsano and Kauli (1982) note that hypogonadism is common in PWS, and suggested that on the basis of a case study precocious puberty may be due to both hypothalamic and gonadal defects, as opposed to just an hypothalamic cause, as previously thought. Other groups have also put forward this theory (Jeffcoate, Laurance, Edwards and Besser ,1980). Costeff, Holm, Ruvalcaba and Shaver (1990) suggest any thyroid problem is secondary to a malfunction in the hypothalamus.

1.6.3.9. Physical features

Short stature is often described in PWS, though as discussed above, there is some debate about whether the short stature is secondary to growth hormone insufficiency. Donaldson et al (1994) note that children with PWS are usually on the 10th centile for height or below, in contrast to non-affected obese children who are usually tall for their chronological age. Butler (1990) notes the lack of growth spurt in adolescence results in PWS affected adults being proportionately smaller than PWS affected children. However short stature is not invariably described in PWS. Harty, Hollowell & Sieg, (1993) report two cases of tall stature in boys with clinical

and genetic diagnoses of PWS. Both children were following the ninetieth centile for height, despite their parents' height being nearer the 50th centile.

As has been described in other genetic syndromes, individuals with PWS are often reported to have a characteristic face. The features include: a disproportionately narrow fore-head, almond shaped eyes, down turned mouth and an abnormal ear shape (Cassidy, 1992, Holm et al, 1993). Butler (1990) notes that only 75% of cases in his review of the literature, had a narrow fore-head or almond shaped eyes but it is not explicit what proportion of cases had only one or both features. 'Sticky' salvia is often reported in PWS affected individuals (Holm et al 1992).

Other physical features frequently noted in PWS include hypogonadism. 90-100% of individuals with PWS are described as showing this feature (Cassidy, 1992, Butler, 1990). Holm (1992) lists it as a major diagnostic criteria. The source of this anomaly is debated above. Small hands and feet are also evident in 70% of typical cases (Holm et al, 1992) as is hypopigmentation in 41% according to Holm et al (1992). A squint is common in PWS, occurring in 60-70% of cases. Scoliosis is apparent in 40-60% of cases (Cassidy, 1992) though other studies describe a lower rate (Holm et al, 1992), and surgery is rarely required (Jones, 1992).

1.6.4 HSS and PWS compared

Having reviewed the literature describing the phenotypic features of PWS, it is clear that there are many similarities with HSS. Though, as we have suggested above, some 'characteristic features' may not be specific to either syndrome. However bearing that in mind, the similarities and contrasts between the two conditions are described below in table 1.6.4.1. The apparent parallels between HSS and PWS need to be examined systematically.

*Table 1.6.4.1: The similarities and differences between PWS and HSS**

Feature	***HSS***	***PWS***
hyperphagia	yes	yes
failure to thrive infancy	yes	yes
hypotonia in infancy	?	yes
short stature	yes	yes
GH insufficiency	yes	?
learning difficulties	yes	yes
self-injury/skin picking	yes	yes
hypogonadism	?	yes
characteristic face	?	yes
oppositional behaviour	yes	yes
obesity	no	yes
overactivity	yes	no
sleep disturbance	yes	yes
genetic anomalies	?	yes

* ? there is debate in the literature or there are no data available

Chapter 2

2.0 Study aims and hypotheses

2.1 Research questions

Following the review of the literature, there are a number of research questions that need to be addressed.

- Though the existing HSS literature clearly shows a strong association between HSS and adversity, studies have drawn this conclusion retrospectively, using rather vague criteria. In the present study we aim to examine psychosocial adversity using systematic measures and objective judgement.
- Second, if we assume stress is an intrinsic part of HSS, without controlling for environmental adversity, it is impossible to conclude confidently that *any* of the HSS features described in the literature are specific to the condition. The existing literature almost invariably lacks any appropriate comparison group.
- Further if we are to suggest that children with HSS are hyperphagic, systematic comparisons between the HSS and another hyperphagic population are required, such as the PWS population. Many other parallels between the features of HSS and PWS became evident in reviewing the literature and these should be examined more closely.
- There does seem to be some evidence that children with HSS often have siblings with similar features. Familial aggregation must be tested systematically and with appropriate comparison groups. Familial aggregation of a syndrome may indicate that there are genetic influences acting on that condition. If there is a genetic explanation, then this might explain why children with HSS are so distinct from other growth retarded children.
- The next step might be to find a genetic marker for the condition. If PWS and HSS have such close parallels in terms of their phenotype, is it possible that the genotype responsible for PWS is also associated with HSS?

2.2 Hypotheses

The following hypotheses aim to cover the issues described above. The hypotheses are described in more detail in the results section. There are four sections, A to D:

A) ***Stress***

This section examines the idea of HSS manifesting in chronic stress.

- The HSS affected children live in conditions of psychosocial adversity.
- HSS care-givers have a characteristically emotionally arousing inter-personal style, or high ' Expressed Emotion'.
- HSS families have a 'distressed' family environment profile.
- The HSS affected children will show an Hypothalamic-pituitary-adrenal (HPA) response to acute stress characteristic of a chronically stressed population.

B) ***The HSS phenotype***

These hypotheses aim to illustrate two issues. The first aim is to document the aspects on which PWS and HSS are phenotypically similar. Second, we aim to identify features that might be viewed as normative stress responses, and those features which are specific to HSS.

It is hypothesised that HSS group profiles will be similar to children with PWS but that HSS profiles will be distinct from the profiles of other stressed children, in terms of:

- cognitive ability and profile
- anthropometry
- infant health
- degree and quality of appetite disturbance (hyperphagia)
- self-reported psychosocial profile
- care-giver reported behavioural disturbances
- care-giver reported psychosocial adjustment
- teacher reported psychosocial adjustment
- the consistency of behavioural disturbance at home and at school
- dysmorphology

C) The siblings:

This section explores familial aggregation. Further in comparing children affected with HSS to their unaffected siblings on a number of independent indicators, further validation of HSS as a discrete syndrome may be provided.

- HSS shows familial aggregation
- children affected with HSS will show relatively poor cognitive ability in comparison to their unaffected siblings
- children with HSS will show relatively poor psychosocial adjustment in comparison to their unaffected siblings
- children with HSS have a lower birthweight than their unaffected siblings

D) Molecular genetic Investigations:

The final section explores the genetic basis to HSS, using molecular genetic techniques.

- The major locus associated with HSS coinherits with the PWS locus, mapped to 15q11-13.

Chapter 3

3.0 Methodology

3.1 Subjects

3.1.1. Groups

3.1.1.1 The index children

There were three groups who will be referred to as the index children.

- Children identified as having Hyperphagic Short Stature Syndrome (HSS). (*n* = 25).
- Children who have Prader-Willi Syndrome (PWS). (*n* =30).
- Children living in chronic stressful circumstances. (stressed). (*n* = 25).

The HSS group will be referred to as the case group and the PWS and stressed groups as comparison groups.

3.1.1.2 The siblings

In addition, the siblings of the index children in each of the three groups were also assessed.

- The siblings of children with HSS (n = 44)
- The siblings of the children with PWS (n= 29)
- The siblings of the stressed children (n = 28)

3.1.2 Recruitment

HSS group recruitment:

Children were recruited via a number of sources[1]. First, through professionals at Great Ormond Street Hospital (GOSH) and other tertiary referral centres. They were referred by endocrinologists, paediatricians, and clinical psychologists. The author contacted a number of professional organisations such as the Thames Community Paediatricians Groups and the Paediatric Endocrinologists Association, requesting cases. We also advertised at conferences and special interest groups such as the British Paediatric Association meeting. Professionals then approached the author with the names of possible subjects.

A second route was using advertisements in women's magazines, asking families to volunteer for the project (see appendix 11). Families were invited to respond in the advertisement; the project procedure and aim was then described by letter or by 'phone.

[1] The group were recruited prospectively for this study and are distinct from the HSS series described in the Skuse et al paper (1996).

PWS group recruitment

50% of the PWS group were recruited through the parental support group, the Prader-Willi Association (UK). Letters were sent via the association's newsletter. A further 26% of the PWS group were members of the association but were contacted through other sources. We wanted to contact a wide population of families who had a child with PWS, not just those who were members of the support group and more likely to be well informed about the condition. 17% were recruited using advertisements in women's magazines, as described above. The remainder were referred through professionals, contacted as described previously. In addition to those professional bodies described in HSS recruitment, Clinical Genetics Society members were also contacted by letter.

Stressed group recruitment:

Stressed children were recruited from three sources. First through the Child Care Consultation Team (CCCT) and Child Sexual Abuse Team (CSAT), Department of Psychological Medicine, at Great Ormond Street Hospital (GOSH). We also contacted five London boroughs to enlist the help of the Child Care Protection Co-ordinators in the Children and Families Units. Information letters and return slips were passed on to candidate families by social workers. We contacted 24 schools for Emotionally and Behaviourally Disturbed children (EBD schools) in the Greater London area. Three schools agreed to send the letters that we provided to families fitting our inclusion criteria, described below. In these cases, family names only became known to the author if the family responded directly. Families recruited through social services and EBD schools were offered fifty pounds in return for participating in the study.

3.1.3 Refusal rate

The recruitment sources for each group are reported in table 3.1.1. Due to the methods of recruitment that we were required to employ, we are unable to report exactly how many families were approached and the percentage of those who agreed to take part. Social services and EBD schools reported that tens rather than hundreds of letters were passed on to families, but it is clear that there was a high refusal rate. This is perhaps inevitable given the circumstances in which the families we were targeting, lived. Of the families we contacted directly (see table 3.1.1), through GOSH, all but one family decided to participate in our study.

Table 3.1.1: Referral source

referral source	*HSS (%)*	*PWS (%)*	*stressed (%)*
endocrinology clinic (GOSH)	44	0	0
CCCT/CSAT (GOSH)	4	0	48
other GOSH clinic	16	10	4
social services	0	0	8
EBD schools	0	0	40
PWS(UK) assoc.	0	50	0
magazine advert	12	17	0
other professionals	24	23	0

3.1.4 Inclusion criteria

We aimed to collect data on children living at home with their permanent care-taker but due to the difficult circumstances in which many of the families lived, there were a number of exceptions. In four HSS cases and one stressed case, children had been removed from home and were accommodated voluntarily or through a Care Order by the time of our assessment. We interviewed the original caretakers in three of these cases. The children had been removed from their home not less than 4 months before the interview. The final two caretakers were unavailable for interview but foster parents and social workers provided information in those instances. A number of children have been removed from home since the time of our assessments. The placement of the children is described more fully in the demographics chapter.

HSS group inclusion criteria

Children were confirmed as HSS cases if their behaviour met the criteria in the diagnostic algorithm, defined by Skuse, Albanese, Stanhope, Gilmour and Voss (1996). Affected Individuals showed at least two of the following behaviours from group A and at least one from group B. Evidence that the behaviours were persistent and enduring was a prerequisite to the diagnosis:

Group A

- gorging and vomiting
- stealing food at home
- stealing food at school

Group B

- stealing food at night or early morning
- hoards food
- forages for discarded food
- eating excessively
- drinking excessively

Further, affected children should be:

- between 3rd and 97th centile for weight (Tanner Whitehouse Standards 1976)
- below the 3rd centile in height (Tanner Whitehouse Standards 1976), or below the 3rd centile in height in relation to parental height, or a consistent height velocity below the 25th centile.

All but two cases fitted this algorithm. Both children's height lay below the 25th centile for height. However when parental height was taken into account, they fitted the algorithm.

PWS group Inclusion criteria

Children in this group were identified as having Prader-Willi Syndrome either, clinically by a paediatrician or clinical geneticist, or using genetic testing. Some children who had a negative result following PWS cytogenetic investigations were included in the study. In up to 40% of PWS cases, the cytogenetic test will not provide evidence of a deletion (Butler 1990). Given the relatively poor sensitivity of the cytogenetics test, we felt it was acceptable to include clinically convincing cases who did not show a deletion using a cytogenetics investigation. An alternative method of diagnosing PWS involves a methylation test which identifies the parent specific methylation state of the PWS critical region. Methylation of a region indicates it is inactive or does not exist, and therefore both uni-parental disomy and a deletion can be detected using this method. The methylation test (Dittrich, Robinson, Knoblauch, Buiting, Schmidt, Gillessen-Kaesbach and Horsthemke,1992 and Buiting et al, 1994) has excellent sensitivity in identifying PWS cases (Gillessen-Kaesbach, Gross, Westerloh, Passarge & Horsthemke, 1995). We did not include any child who had had a negative result from the methylation test.

Stressed group Inclusion Criteria: Social Services contact and chronic stress

All the children in the stressed group came from families who had been identified by social services as living in circumstances of chronic intra-familial stress. Children who had had one incident of sexual abuse for example, were not deemed to be chronically stressed.

All of the stressed group, on whom we had full details, were either on an 'at risk register' or social services had 'grave concern' about their present family circumstances. The remaining

children (n = 10) were recruited through the EBD schools. A condition of the EBD schools' participation in our study was that the precise nature of the families' circumstances would remain undisclosed. However, following careful consultation with the schools and the social workers involved in recruitment, we are confident that the remaining families fit our criteria.

The type of stress reported is illustrated in table 3.1.2. The categorisations provided are made on the basis of social services reports, or following consultation with the child protection teams (CCCT and CSA) at GOSH. Some children appear in more than one category. By definition, all abuse experienced includes an element of emotional abuse, but here only the primary categories of abuse are reported.

Table 3.1.2: Categories of chronic stress (stressed group only)+

	cases on whom full details were available (social services and GOSH records)			
case	*physical abuse*	*emotional abuse*	*sexual abuse*	*neglect*
JC				✓
GL	✓			
GA				✓
RB		✓		
TA				✓
PB				✓
DS	✓	✓		
LR			✓	
CH	✓	✓		
MW				✓
HE			✓	
AM	?			
SH	✓	✓		
SS		✓		
VS			✓	
	*cases recruited from EBD schools**			
case	*physical abuse*	*emotional abuse*	*sexual abuse*	*neglect*
JP	✓	✓		
TJ		✓	?	
NM		✓		
BF				?
GP				?
CJ		✓		
NB				✓
EB	✓	✓		
RG		?		
NS	✓	✓		

** these classification were made on the basis of parental information and after consultation with Professor Skuse, Consultant Psychiatrist*

+ ? œnotes abuse is suspected, not confirmed

3.2 Measures and assessments

See the appendices for the unpublished measures listed below.

3.2.1 Anthropometry

Anthropometric measures were obtained using standard clinic equipment by trained personnel. We used the Tanner-Whitehouse (1976) method to calculate weight and height. The 'Castlemead Growth Program' (1993) was used to convert heights and weights into standard deviation scores, corrected for age. A standard deviation score of -1.88 corresponds approximately to the 3rd centile.

3.2.2 Cognitive Ability

The short form of The Wechsler Intelligence Scales for Children III UK (Wechsler 1992) (WISC III UK) were used to assess cognitive ability in children over the age of 6 years. The short form of the WISC-R has been shown to be valid for research purposes (Hunter, Yule, Urbanowicz and Lansdown, 1989). Children aged 3 to 6 years were tested using the equivalent cognitive test for younger children, the Wechsler Pre-school and Primary Scale of Intelligence - Revised (Wechsler, 1990) (WPPSI-R). Previous piloting using the Kaufman Assessment Battery for Children (Kaufman and Kaufman 1983) proved unsatisfactory, in terms of the cultural knowledge of North America required to address the attainment scales. As both Wechsler scales have recently been standardised in the UK, this confounding factor was avoided. In both tests four subscales were selected: two of which were performance scales (picture completion and block design), two of which were verbal sub-scales (vocabulary and similarities). These sub-scales were selected as they correlated most highly with full scale and either verbal or performance IQ ($r = .60$ to $.85$) in the WISC. We were able then to prorate these scores to calculate verbal, performance and full-scale IQ. Test-retest reliability averaged across all age groups, for each of the four sub-scales in the WISC III UK range from .77 to .87 and .84 to .86 in the WPPSI. Kaufman (1979a) demonstrated the construct validity of the WISC in identifying children with learning difficulties. Wechsler described similar properties for the WPPSI-R (Wechsler, 1990). Training in reliable administration and scoring of both tests was completed under the supervision of a principal clinical psychologist at Great Ormond Street Hospital.

3.2.3 Psychosocial profile (child report)

3.2.3.1 The Child Assessment Schedule (Hodges 1978)

The interview was administered to all children over the age of 6 years. The most recent version of the CAS was published in 1986 and may be used by non-clinicians to diagnose using DSM III criteria, but because of its relative complexity is not appropriate for children under the age of 10 years. The 1978 CAS does not allow a diagnosis but is suitable for children as young as 6

years old. (Kay Hodges, personal communication). Instead, it produces symptom clusters corresponding to the major disorders described in DSM III: attention deficit (with and without hyperactivity), undersocialised conduct disorder (aggressive and unaggressive type), socialised conduct disorder, separation anxiety disorder, overanxious disorder, oppositional disorder and depression. The items are dichotomous, behaviour is rated as being present or absent. The interview falls into two parts, first using verbal responses from the child (191 items) covering various content areas such as family, friends, school and worries. The remaining 54 items are based on observational judgements made by the interviewer (JG). The 1978 CAS has good inter-rater reliability (between four raters) with correlation coefficients ranging from .84 to .92 (Hodges 1978). Its validity is demonstrated using three groups: normal control, clinic out-patient and inpatient group comparisons: total score, 7 of 11 content areas and symptom complex scales (with the exception of overanxious disorder and depression) differentiated the groups (Hodges 1978). Significant correlations with the Child Behaviour Checklist (Achenach, 1991) and the Children's Depression Inventory (Kovacs 1981) provide evidence for its criterion validity. More recent figures expand upon these initial data, confirming the favourable psychometric properties of the interview as compared to other child assessment interviews (Hodges, 1993) such as the Diagnostic Interview Schedule for Children - Revised (Shaffer et al 1988).

Training in the administration and scoring of the CAS was completed under the supervision of Jackie Smith a research psychologist working at University College, London, who trained with Kay Hodges and is establishing British norms for the scale. Following piloting the 'Thought Disorder" section was dropped from the CAS interview, as it proved unacceptable to a number of children . After completing training, reliability was established. 10 pilot interviews were administered to in-patients and out-patients attending the Department of Psychological Medicine, GOSH. Kappa coefficients were used to calculate reliability for each individual child report item in the CAS. A kappa value of .4 to. 59 is acceptable, while kappas of .6 to. 74 are considered to indicate 'moderately good' reliability. Those kappa values above .75 are considered excellent. 90% of the kappas were 1.00 (perfect agreement between the two raters), a further 2% were in the band 0.8 to 0.89, 2.5% were between 0.7 and 0.79, 4% were between 0.6 and 0.69, and the final 0.5% were in the 0.5 to 0.59 band. Kappas ranged from 1.00 ($p < 0.00$) to 0.58 ($p = 0.06$). with an average of 0.97.

3.2.4 Psychosocial profile (care-giver report)

This was assessed using a number of individual measures:

3.2.4.1 The Hyperphagic Short Stature Diagnostic Interview (HSSDI)

The HSSDI interview (Gilmour and Skuse 1993) was designed for the study specifically to identify children with the HSS behavioural phenotype. Because of the distinct nature of the issues to be addressed, for example type and severity of hyperphagia, no existing published measure was suitable. The HSSDI documents behaviour over a wide range of functioning and assesses both current and previous behaviour. The interview takes into account the potentially episodic nature of the condition, and allows a developmental perspective on behaviour.

The interview is semi-structured, requiring parents to provide specific examples of their child's behaviour. Ratings (0-3) were justified on the basis of actual reported behaviour, rather than parental opinion or generalisations. The behaviours described were rated against existing anchors specified in the interview. This method of interviewing is more consistent than asking parents to make their own individual judgements about the relative severity or abnormality of their child's behaviour. Frequency, severity and the context in which behaviour occurred were noted. Where possible ICD-10 criteria were employed.

The initial version of the interview was drafted on the basis of ten years clinical experience with the condition. Previous data illustrate the predictive validity of this instrument. It was used to differentiate HSS cases from unaffected comparison children. The cases, identified only on the basis of the interview, were demonstrated to have physiological correlates (reversible growth hormone production) which were not evident comparisons (Skuse et al 1996).

3.2.4.2 The Child Behaviour Checklist (CBCL) (Achenbach 1991a)

This is a questionnaire completed by parents. It has 113 items (rated 0-2) , covering a wide range of internalising and externalising difficulties. Individual items converge into scale scores: activities, social, school, withdrawn, somatic complaints, anxious/depressed, social problems, thought problems, attention problems, delinquent behaviour, aggressive behaviour and sex problems. The scale scores reduce further into total competence, total problem and internalising and externalising scores. The instrument has separate norms for girls and boys. Reliability was calculated across a 7 day interval with mean rs ranging from .7 to. 93 for the scale scores. Reliability coefficients for the internalising and externalising scores were .89 and .93 respectively (Achenbach, 1991a). The measure has also been demonstrated to have long term stability (r of .70 and .86 for internalising and externalising scores). Construct validity was illustrated, for example, by comparing the Connors Parent Questionnaire (Connors 1990) and the Quay Peterson Revised Behaviour Problem Checklist (Quay Peterson 1987) with CBCL total problem

score, resulting in correlations of .82 and .81 respectively (Achenbach, 1991a). All scales in the questionnaire have been shown consistently across age groups and sex to differentiate between referred and non-referred groups at an alpha of 0.01 (Achenbach 1991a).

3.2.5. Psychosocial profile (Teacher report)

3.2.5.1 The Teacher's Report Form (TRF) (Achenbach 1991b)

This is the parallel form of the CBCL, with 113 items (rated 0 -2) rated by teachers, tapping into adjustment at school. As with the CBCL, these items converge into a number of scales: academic performance, working hard, behaving appropriately, learning, happy, withdrawn, somatic complaints, anxious/depressed, social problems, thought problems, attention problems, delinquent behaviour, aggressive behaviour. As described above, these scaled scores further reduce into: total adaptive, internalising, externalising and total problem scales. The CBCL and the TRF may be used together to compare behaviour across home and school contexts. Similar psychometric properties are described in the TRF as compared to the CBCL. Reliability over a 15 day interval ranged from .78 to .96 (Achenbach 1991b). Criterion validity is demonstrated using the Connors Revised Teacher Rating Scale (Goyette, Connors Ulrich, 1978) with an r of .83 between total problem scores. Only the somatic complaints for 12-18 year old boys does not differentiate between referred and non-referred samples, though it is approaching significance ($p = 0.066$). All other scales differentiate between referred and non-referred groups across age groups and both sexes.

3.2.5.2 Difficult Behaviour Questionnaire (DBQ) and GOSH School Report

These instruments are questionnaires[2] (Skuse 1987), completed by teachers covering specific aspects of the child's emotional and behavioural adjustment, including the HSS phenotype. The questionnaires are used routinely in both research and clinical contexts to gather systematic information on children attending the Department of Psychological Medicine, GOSH.

3.2.6 Child Health History

The Child Health History is a checklist questionnaire completed by care-givers. Each of the 45 items had originally been part of the HSSDI administered in interview form, but during piloting we found that parents preferred answering such straightforward questions in questionnaire format as it was less time consuming. Items were rated as either true or false, or care-givers were asked to provide information such as the child's birth weight.

[2] Some items in these instruments are based on questionnaires developed at the Institute of Psychiatry, London

3.2.7 Parenting style and family environment:

This was assessed using two different instruments:

3.2.7.1 The Camberwell Family Interview (CFI) (Vaughn and Leff 1976b).

CFI probes were incorporated into the HSSDI. The interview contents were approved by Christine Vaughn. These probes are not mandatory but are used at the discretion of the interviewer (JG) to elicit the attitudes and feelings of the care-giver about the child and the child's behaviour. Ratings of expressed emotion (EE) are subsequently made from the recorded discourse. The author completed the CFI training course run by Christine Vaughn at the Institute of Psychiatry, London, covering the administration of the CFI and the rating of expressed emotion.

The rating of EE produces a number of scales*: critical comments* and *positive remarks* (simply frequency counts from the interview) and *emotional over-involvement* (*EOI*), *hostility* and *warmth*, all of which are global ratings. The scales are not mutually exclusive.

- A *critical comment* is 'a statement which, by the manner in which it is expressed, constitutes an unfavourable comment upon the behaviour or personality of the person to whom it refers' (EE training manual). It is rated both on the basis of the content of speech and the tone of voice. For example ' I can't stand it... it makes me feel sick'.

- *Positive remarks* are statements which show praise approval or appreciation of the child. 'She's a very bright kid' would constitute a positive remark.

- *Hostility* describes negative generalised or rejecting comments about the child as a person, rather than the child's behaviour. For example 'I hate to sit at the dinner table with him'. It is rated from 0 to 3.

- *EOI* is rather more complex, rated from 0 to 5. This category covers parental over-concern over a wide range of behaviours and may include self-sacrificing behaviour, a statement of attitude concerning the impact of a child's behaviour on the relative's life or exaggerated emotional response. For example, a parent who would never leave his/her child with an alternative care-taker for an evening would be considered to be showing self-sacrificing behaviour. Responses are rated in context, and therefore a child's developmental level must be taken into account when judging whether parental behaviour is appropriate. This is discussed further below.

- Warmth, rated from 0 to 5, indicates the warmth expressed concerning the child. It is judged on the basis of the content of the comment and tone of voice. This might include empathy, for example ' he takes food because he feels hungry... it's hard for him'.

From these scales, care-givers are rated as either high or low in terms of their expressed emotion. Care-givers who score over 3 on EOI or are rated 1 and above on hostility, or make 6 or more critical comments are regarded as high EE.

Patients with a wide variety of organic and psychological conditions are more likely to experience a poor outcome living with high EE relatives. In other words, high EE may be regarded as a risk variable (Vaughn 1989). Though these issues are pertinent to this study, more specifically, we wished to use the EE rating as a measure of the 'emotional temperature' surrounding the child. (Vaughn 1989). Therefore EE is a valid and quantifiable measure of intra-familial stress.

The ratings of EE reported in this study were completed by a family therapist, also trained by Christine Vaughn. The rater was experienced in rating EE in children and families with eating disorders. Ratings were made from audio tapes and transcripts of the interview, blind to case status. The only information made available to the rater was the child's IQ and age. With these data, the rater was able to make objective judgements about the degree of protection necessary for a child of any given age, bearing in mind their developmental abilities. This is crucial for an accurate rating of EOI. We categorised children as in the normal range (IQ of 71 and above), having borderline or moderate learning difficulties (IQ of 70 to 51) or severe learning difficulties (IQ below 50). Children with mild or moderate learning difficulties were not regarded as having particular child protection needs. Learning difficulties of this degree have been labelled as having a '6 hour retardation' (Kushlick & Blunden, 1974), in other words their disabilities surround educational issues rather than *social* functioning. It is the issue of social functioning that relates to the concept of EOI. Only those children with severe learning difficulties were judged to require protection beyond what one may expect in normal children of equivalent age.

3.2.7.2 The Family Environment Scale (FES) (Moos & Moos, 1986).

Caregivers completed this questionnaire comprising 90 items describing the social climate in the family. There are ten sub-scales each of 9 items covering relationship dimensions (cohesion, expressiveness, conflict), personal development dimensions (independence, achievement orientation, intellectual-cultural orientation, moral religious emphasis) and family structure dimensions (organisation and control). Normative data were gathered for 1625 families, 500 of whom were 'distressed'. Test-retest reliability ranges from .68 to .86 in each of the sub-scales

(Moos and Moos, 1986). The assessment discriminates between abusive and non-abusive families. Families with a history of abuse report significantly more conflict and less cohesion, expressiveness, (Perry Wells and Doran 1983). Further the FES may be used to identify parenting attitude (Ollendick, Laberteaux and Horne, 1978). The scale has also proved informative differentiating families who have a child with learning difficulties, chronic illnesses, eating disorders and delinquent adolescents (Moos and Moos, 1986).

3.2.8 The Sibling Checklist

We developed a Sibling Checklist which is an abbreviated version of the HSSDI. It was administered by the author to the principal care-taker, using similar criteria as the HSSDI, but the gradation of response was simply that behaviour was judged to be present or absent. There were 27 items, and on the basis of this we were able to judge whether a child fitted the HSS behavioural phenotype. The distinctive nature of the behavioural phenotype allows identification to be made following such a brief assessment. The HSSDI, provided additional information, important for more complex inter-group comparisons.

3.2.9 Dysmorphology

Each PWS and HSS child was photographed using a Cannon EOS 500 camera in order to identify any dysmorphology characteristic of HSS.

3.2.10 Physiology

3.2.10.1 Salivary Cortisol

Comparison group (salivary cortisol only):

20 normal children aged 8 to 9 years (of whom 12 were boys) provided salivary cortisol samples. They were recruited from a primary school. Parents were informed by letter of our study. This group provided normative data for comparison purposes. The step was administered at 1pm in an exercise in which all 20 children participated simultaneously. The procedure was exactly as described below.

Cortisol levels were assessed using saliva assays, giving a measurement of cortisol secretion following an acute stressor. Salivary cortisol is both an accurate measure of plasma free cortisol levels (Laudat, Cerdas, Fournier, Guiban, Guilhaume and Luton, 1988 and Vining, Robynne, McGinley, Maksvytis & Ho, 1983) and a more attractive option than venipuncture in assessing children as it is non-invasive. This was particularly crucial as we aimed to take a series of assays over a short period of time. Both psychological and physical stressors have been demonstrated to increase salivary cortisol levels significantly from baseline (Kirschbaum & Hellhammer, 1989), but ethically it is more acceptable to induce physical rather than psychological stress on

children. We choose The Harvard Step Test (Kirkendal et al 1987) protocol as it was a simple sequence and procedure. The original protocol, employed in piloting, did not increase heart rate adequately and therefore we increased the rate of stepping from 30 complete steps (both feet up onto the step and both feet back on the floor) per minute for 5 minutes to 60 steps per minute. We aimed to raise the child's heart rate to 150 bpm. At this level and above, we expected to demonstrate an increase in salivary cortisol levels (R Laign, Respiratory lecturer, GOSH personal communication).

3.3 Procedure (psychological assessments)

The procedure was identical for each group, though families were seen most often at home and in one HSS case, data collection was completed during an in-patient admission to Great Ormond Street Hospital. The author and a research psychologist (JN) completed the assessments together.

- All assessments described above were administered for the index children
- Siblings were assessed using the CBCL (Achenbach.1991a), the WISC-III-UK (Wechsler, 1992) and the Sibling Checklist

First families were given the appropriate information sheet (see appendices 6-9) and gave written consent for their participation. Children gave verbal consent. Where possible the data collection was organised so that while JG interviewed the care-taker, JN assessed the index child or siblings and vice versa. The complete assessment was usually completed within three hours. The interview began with a verbal explanation of the project to the family. We used separate rooms to interview parents and children. At the start of the session the index child was told:

We want to do some games and puzzles with you first and then do the same games and puzzles with your brothers/sisters. After the puzzles we want you to jump up and down on our step for five minutes and then ask you to spit into a tube. This means that we can look at the effect of exercise on your body.

During this time JN administered the IQ test to the index child, and then completed the Harvard Step Test. The protocol is described fully below. Simultaneously JG administered the HSSDI, completed the Sibling Checklist and gathered a family history with each care-taker. JG then administered the CAS with the index child . At the start of the session, the child was told:

I want to ask you some questions about how you're getting along at school, what you like to do with your friends - that sort of thing. There are no right or wrong answers and I'm not trying to catch you out, I just want to find out how you are getting along. I won't tell anyone at home or anyone at school. This is between me and you, but you can tell anyone you want. I want to tape our conversation but this is only to help me remember what we have talked about, I won't let anyone listen to the tape, and we can switch off the tape recorder at any time.

While JG was administering the CAS, JN met with the care-taker(s) and explained the questionnaires. Parents had the option to complete the questionnaires verbally as some parents had limited reading and writing skills. On some occasions parents wanted to complete the questionnaires after we had completed our visit. In these cases we provided a pre-paid envelope for the completed questionnaires. Figure 3.3.1 shows the time-table of a typical data collection session in which the index child had two siblings.

Figure 3.3.1: The assessment time-table

time (mins)	*index child*	*sibling(s)*	*care-takers(s)*
0	WISC/WPPSI (JN)		HSSDI (JG)
10			
20			
30			
40	saliva sample 1 (JN)		
50	step test (JN)		
60	saliva sample 2(JG)	WISC / WPPSI(JN)	
70	saliva sample 3(JG)		
80	saliva sample 4(JG)		
90		WISC /WPPSI(JN)	sib check-list (JG)
100			
110	saliva sample 5(JG)		family history (JG)
120	CAS (JG)		questionnaires (JN)
130			
140			
150			
160			
170			
180			

**The shaded area indicates the family member is occupied.*

3.4. Procedure (salivary cortisol)

Equipment

- 'Reebok" aerobic step, height set to 6 inches
- Polar Heart Rate Monitor which gives a continuous reading
- music at a speed of 120 beats per minutes (bpm).
- stop watch
- sherbet sweets: ingredients: sucrose, citric acid
- 1" diameter flat bottom tubes

First the child provided a base-line sample of saliva, the time of the sample was noted. In all but 2 HSS, 3 PWS and 4 stressed cases, testing took place between 12.30 and 3.30 pm. (The exceptions were tested between 10.30 am and 12.30 pm). At this time, according to circadian variation, normal individuals show falling cortisol levels (Laudat, Cerdas, Fournier, Guiban, Guilhaume and Luton, 1988). We encouraged the child to have a small amount of sherbet to induce salivation with each sample. The Heart Rate Monitor was secured around the child's chest, using one of the variable width chest bands. The child's base-line heart-rate was recorded. The step procedure was demonstrated; beginning with two feet on the floor, the right foot was placed on the step, followed by the left foot so that both feet were on the step; then the right foot was placed back on the floor, followed by the left foot. Music maintained the child's interest and encouraged stepping to continue at the appropriate frequency. The step exercise lasted five minutes. Immediately after the step exercise was completed, the child's heart rate was recorded. 10, 20, 30 and 60 minutes after the step exercise was completed, further saliva samples were collected into appropriately marked tubes.

The series of salivary cortisol samples were analysed at the Mass Spectrometry and Physiological Biochemistry Unit, at the Institute of Child Health. After deep-freeze storage, which eliminates problems with viscosity (Riad-Fahmy, Reid, Walker & Griffiths, 1982), assays were analysed using the Diagnostic Products Corporation 'Cortisol Double Antibody' radioimmunoassay, designed for the quantitative measurement of cortisol. It has been demonstrated to be accurate over a broad range of cortisol values. Cortisol was measured using a standard curve constructed in synthetic saliva buffer. The buffer was based on a method of Kidd EAM which is known commercially as VA oralube. It was diluted 1:4 with PBS/G before use .

3.5 Procedure (molecular genetics)

3.5.1. Subjects

Only index children affected with HSS and a number of their siblings were tested using the molecular genetic techniques described below. Children in the stressed and PWS groups were not involved in this part of the study

3.5.2 The blood samples

All genetic analyses were carried out at the Clinical Molecular Genetics Laboratory, at the Institute of Child Health. The author observed each stage of the process. Venous blood samples were taken by General Practitioners, and sent by post to the laboratories, or taken by the ward staff on the Frederick Still Ward, at Great Ormond Street Hospital. 5-10 ml of venous blood was collected into plastic tubes containing ethylenediamine tetraacetate (EDTA) which is an anticoagulant. Samples were labelled in the laboratory according to the standard procedure. Blood was then stored at -70 degrees centigrade until DNA extraction and analysis.

Two different techniques were employed.

- methylation status studies
- sibling pair linkage analysis

3.5.3 Methylation status studies

The methylation status test (Dittrich, Robinson, Knoblauch, Buiting, Schmidt, Gillessen-Kaesbach and Horsthemke, 1992) is 99% sensitive (Reis et al, 1994) in detecting the Prader-Willi syndrome genotype, and therefore was considered the first step in testing the hypothesis of coinheritance between the HSS and PWS' loci. The Prader-Willi syndrome critical region, on the long arm of chromosome 15, is imprinted. In other words, unlike most genes where both the paternally and maternally derived alleles are actively expressed, in imprinting only one of the two alleles is expressed. In the case of the Prader -Willi imprinted region, *only* the paternal allele is expressed in normal development. Individuals who have only the maternal allele (due to a deletion on the paternal chromosome), or two maternal alleles (uni parental disomy, UPD) at 15q11-13 will have Prader-Willi Syndrome (The American Society of Human Genetics, 1996).

The key to identifying the PWS genotype lies in accurate labelling of the parental origin of each allele. Methylation status tests allow accurate identification and avoid the need for dosage analysis of deletions which can be difficult to interpret. This is possible because the enzymes used in this process, are sensitive to the methylation status of the allele. Methylation reflects whether a gene is active or inactive. An enzyme 'recognises' particular sequences of DNA and

will cut the strands at these recognised sites depending on whether or not they are methylated. By studying the relative length of the fragments, it is possible to ascertain their parental origin and to demonstrate the existence of deletions or UPD.

In the present study, initially, the PW71b (D15S63) probe was used. In these cases a Southern Blot (which transfers the DNA on to a nylon filter) was made of DNA digested with the enzyme HindIII, and HpaII which is a methylation sensitive enzyme cutting only when DNA is unmethylated. In normal individuals two bands of differing length are present, indicative of each parent's contribution. The shorter fragment (4.7 kb) is derived from the paternal chromosome and the longer 6.6 kb fragment from the maternal chromosome. In individuals with PWS, who have a deletion or mutation of the paternal allele or UPD, in the vast majority of cases, only the 6.6 kb band will be present. A newer probe (L48.25X) (Buiting, Dittrich, Robinson, Guitart, Abelivich, Lerer and Horsthemke, 1994), which detects a sequence in the exon alpha of the candidate PWS gene SNRPN, was used in a number of cases. Because this probe is closer to the candidate gene SNRPN than PW71b, the test is less likely to produce false negative results. For this probe the southern blot of DNA was digested with the enzymes XbaI and NotI (which is methylation sensitive). The 4.2 kb fragment is maternally derived, while the 3.0 kb and 0.9 kb fragments are paternally derived. In other words, individuals with PWS would show the 4.2 kb fragment only, where L48.25X is applied reflecting the methylation status of the exon alpha of SNRPN (Buiting et al, 1994).

The PW71b/ L48.25X probe protocol :

A. Adding the enzyme to DNA:

1. The DNA and the buffers (which maintain a constant pH) are removed from the freezer to thaw
2. 12-14.5 ul sterile water and 4 ul of buffer is added to the eppendorf (tube)
3. 20 uls of DNA sample is added
4. The DNA (or digest mix) is mixed and spun down in a microfuge
5. 1.5-4 ul of the appropriate enzyme is removed from the freezer and added to the digest and incubated in a water bath at the appropriate temperature for the enzyme (usually 37 degrees centigrade for HpaII).

B. 2 hours before the agarose gel is run, it is prepared using the following method:

1. Agarose gel at 0.8% is prepared, and buffer added
2. Once the gel solution is dissolved, ethidium bromide is added (5 ul per 100 ul gel solution)
3. Once cooled, the gel is poured into the tray, and the combs are inserted to make wells (these keep the digests separate). After 40 minutes the gel is set.
4. A tank is then connected to a power pack, so that the DNA runs through the gel to the anode (from negative to positive).
5. The tank is filled with electrophoresis buffer . The gel is placed into the tank and the combs are removed.
6. The appropriate volts: amps ratio is used (dependent on the size of tank).

C. The gel is then loaded with the DNA digest using the following method:

1. Marker DNA such as lambda/HindIII is removed from the freezer. This acts as a reference point in order to calculate the size of the DNA fragments in the individual being tested.
2. The digests are spun down
3. 10 ul of loading dye is added to each sample (this marks the track of DNA, which can be viewed under UV light)
4. The sample is injected into a well in the agarose gel
5. 40 ul of marker DNA is added to one well
6. The tank current is then switched on and run overnight.

D. The next step is Southern blotting:

1. The gel is photographed, to check that is has run properly.
2. The gels are denatured, (the double helix DNA is split apart into single strands) using alkali.
3. The blotting tray is prepared
4. The gel is laid on the blotting tray, a wet Hybond N+ nylon membrane is laid over the gel with paper towels placed on top to draw the fluid up. The blot will run for 2-12 hours.
5. The nylon membrane is soaked in 0.4M NaOH to fix the DNA to the membrane and rinsed thoroughly in 2 x SSC (twice the standard concentration)

E. A probe for example PW71b is labelled with radioactivity. The radioactive label allows the fragments to be detected by an X ray plate.

1. The non-specific sites on the DNA are blocked (pre hybridisation). The probe is then added to the solution and filter.
2. Hybridisation of single stranded radioactive probe and DNA is achieved by incubating at approximately 65 degrees centigrade overnight.
3. The filter is then washed thoroughly in RT x 3 SSC, three times, 0.1% SDS then in 0.5 SSC, 0.1% SDS, so that the probe is only attached to the matched piece of DNA on the filter.
4. The filters were then exposed to x ray film.

Shorter fragments travel more quickly in the agarose gel, as they have lower molecular weight. This means that the shorter the length of DNA fragment, the further down the gel it will appear. Following this procedure, two bands of differing length (4.7 kb and 6.6 kb, for example) will be evident on x ray film if the individual does not have PWS. The probe will have identified each of the alleles, one from each parent. The methylation sensitive enzyme means that each parent's allele will be a different length. In PWS affected individuals, the absence of the shorter fragment (4.7 kb) will confirm that the paternal allele is missing.

3.5.4 Sibling pair linkage analysis

This method is based around the premise that loci close to one another on the chromosome will stay together during meiosis, and that loci further apart have a higher chance of recombining during meiosis. Linkage does not require that the disease loci has been identified, but only that a marker, close to the disease loci on the chromosome, has been identified. The method requires DNA from at least two affected siblings. Ideally DNA from both parents and all siblings both affected and unaffected with the condition should be available. Where two or more siblings are affected with a condition, it is likely that that they will share the same marker alleles as they are linked to the disease loci and are unlikely to have become separated during meiosis. The more tightly linked the markers are (or closer on the chromosome) to the critical region of the condition, then the greater likelihood that affected siblings will share the marker alleles in common. On the same basis, unaffected siblings will be relatively *unlikely* to have inherited the same marker alleles as their affected siblings. Accurate sibling pair linkage studies are dependent on identifying markers which are tightly linked to the true critical region of the condition being studied. In the case of PWS, there are a number of markers covering much of the 15q11-13 region, and therefore sibling pair linkage studies are a relatively accurate method

of testing the coinheritance of the HSS and PWS loci (Mutirangura, Greenberg, Butler, Nicholls, Chakravarti and Ledbetter, 1993).

The PWS markers (Mutirangura et al 1993) used in this study capitalise on the variable number of CA repeat DNA sequences across the population, within a marker region. These repeats do not influence phenotypic expression in the population. Different lengths of DNA (due to the different numbers of CA repeats) can be identified as coming from different parents, and therefore the pattern of allele inheritance can be detected. The more polymorphic the region, or variable within the population, the more likely that one individual will have different lengths of CA repeat on each allele. Further, it is also more likely that each parent will have different lengths of allele. The greater the variability of an allele within a population, the more informative it will be in linkage analysis. CA repeat markers, like those used in the present study, are useful as they are highly polymorphic or variable. The aim is to identify a high coincidence of marker alleles in affected individuals, and a low coincidence in unaffected.

Four markers covering different parts of the critical PWS region were used: IR4, D15S210, GABRB3 and MS14. The same protocol was followed for each marker.

Sibling pair linkage protocol

Buffer, enzyme nucleotides and primers are added to the DNA. The PCR method is as follows:

1. DNA is denatured at high temperature
2. Oligonucleotide primers are annealed at low temperature
3. The new strands are synthesised using Taq polymerase, which stays stable at high temperatures (up to 95 degree centigrade).

The PCR process is repeated for approximately 25 cycles, resulting in amplification of the target DNA which allows a greater resolution of the CA repeat region. The PCR product is then run on a PAGE denaturing sequencing gel and then the filters are exposed to x ray film.

The process is repeated for each of the four markers. Each marker identifies a pair of alleles so in all eight alleles per individual can be illustrated on x ray film. By convention the longest fragment is labelled 1, the next shortest 2 and so on. The patterns of allele inheritance is described across the critical PWS region and so linkage can be explored in affected sibling pairs.

Chapter 4

4.0 Results

4.1 Statistical issues

Power

There are a number of hypotheses which predict the null hypothesis, that there will be no differences between groups. However, given the small sample sizes, we must be aware that there is a risk of making a type II error. In other words, we may report that there are no significant differences between the groups, as our hypothesis predicts, but this may be an artefact of small sample size and consequent low power, rather than any true non-significant differences. Small sample sizes may mean that we do not have the power to detect significant differences that do exist. Cohen (1992) notes the importance of power calculations, in reference to this particular issue. He notes that conventionally, the specification for power is set at .80. Of fundamental importance is the population effect size. He suggests that a 'medium effect size' is one in which there is a perceptible difference, while large differences are described as 'noticeably larger' (p156). We would argue that one must predict an additional degree of difference in identifying clinical differences, beyond statistical significance. It seems most appropriate to predict a 'large' population effect size, and this should be the criteria against which we set all our analyses. The key issue here is the sample size required to detect large effects. Cohen calculates that using an ANOVA to compare three groups, with the alpha set at 0.05, 21 cases in each group are required to detect a large effect.

Post hoc tests

In each case we used Sheffe post hoc tests, which take in account multiple comparisons and is therefore a more conservative test than the Least Squared Significance test, for example.

Multiple comparisons

Where an excessive number of statistical comparisons are performed on the same data set, there is an increased chance of making a type I error. In these cases a Bonferroni correction was applied (Bland and Altman, 1995).

Statistical testing

Parametric statistics were used where variables were interval or ratio scale. Non-parametric statistical tests were employed for ordinal and nominal variables.

***Table notation*:**

Many of the tables contain numerous figures, making them hard to read. All means that are significantly different from one another are high-lighted in red. There is an example below:

variable	*HSS*	*PWS*	*stressed*
X	1.2	6.8	8.2
Y	3.5	3.5	3.8
Z	5.8	9.4	15.2

This means that on variable X, the HSS group is significantly different from the stressed group. On variable Y, there are no significant group differences. Each group is significantly different from one another on variable Z (in some cases it means that, for example, the stressed group are significantly different from both the HSS and the PWS group, but the PWS and HSS groups are not different from one another). All significant p values are also in red.

4.2 Demographic variables

The families' demographics are described in some detail as these issues are closely associated with parenting and family stress, a central theme in this thesis.

4.2.1 Socio-economic status

The socio-economic status (SES) of the families was balanced across groups, but no attempt was made to match the groups pair-wise. SES is described separately for each parent as there were a number of single parents in each group. Where, for example, an index child's biological mother began a new relationship and her partner lived with her, he would become a substitute father to her children. For demographic descriptions we refer to the new partner as 'father'. However, where biological or genetic issues were involved, only biological parent's data were used. The precise family composition details are described below.

Education:

No significant differences were reported in terms of mothers' educational level (tables 4.2.1. and 4.2.2). Tables 4.2.3 and 4.2.4 describe the educational levels attained by fathers. A similar, comparable pattern between groups is evident.

Table 4.2.1: Mother's education :group means

	CSE		*O levels*		*A levels*	
group	*mean*	*sd*	*mean*	*sd*	*mean*	*sd*
HSS	0.86	2.35	0.62	1.83	0.10	0.3
PWS	1.92	2.74	1.80	2.38	0.33	1.11
stressed	1.26	2.30	1.00	2.30	0.00	0.00

Table 4.2.2: Mother's education: ANOVA analyses

variable	*source*	*df*	*ss*	*ms*	*F ratio*	*F probability*
CSE	*Between Groups*	2	13.73	6.86	1.11	0.34
	Within Groups	67	414.85	6.19		
	Total	69	428.58			
O levels	*Between Groups*	2	16.99	8.49	1.75	0.18
	Within Groups	67	324.95	4.85		
	Total	69	341.94			
A levels	*Between Groups*	2	1.48	0.74	1.49	0.23
	Within Groups	68	33.81	0.50		
	Total	70	35.29			

Table 4.2.3: Father's education: group means.

	CSE		*O levels*		*A levels*	
group	*mean*	*sd*	*mean*	*sd*	*mean*	*sd*
HSS	1.21	3.24	1.60	3.11	0.53	1.13
PWS	1.00	2.22	0.59	1.70	0.33	0.97
stressed	1.19	2.54	0.13	0.52	0.00	0.00

Table 4.2.4: Father's education : ANOVA analyses

variable	*source*	*df*	*ss*	*ms*	*F ratio*	*F Probability*
CSE	*Between Groups*	2	0.39	0.19	0.03	0.97
	Within Groups	41	296.79	7.24		
	Total	43	297.18			
O levels	*Between Groups*	2	16.97	8.49	2.01	0.14
	Within Groups	44	185.45	4.21		
	Total	46	202.43			
A levels	*Between Groups*	2	2.18	1.09	1.46	0.24
	Within Groups	45	33.73	0.75		
	Total	47	35.92			

Parental occupations were also equivalent across the groups for both mothers and fathers. These are reported in tables 4.2.5, 4.2.6., 4.2. 7 and 4.2.8.

Table 4.2.5: Mother's occupation (current or last paid position):group means

HSS		*PWS*		*stressed*	
occupation	*%*	*occupation*	*%*	*occupation*	*%*
intermediate/ managerial	4.3	*intermediate/ managerial*	3.7	*intermediate/ managerial*	0
skilled/ non-manual	8.7	*skilled/ non-manual*	18.5	*skilled/ non-manual*	20
skilled manual	0	*skilled manual*	18.5	*skilled manual*	4
partially skilled	17.4	*partially skilled*	18.5	*partially skilled*	12
unskilled	43.5	*unskilled*	22.2	*unskilled*	56
unemployed	8.7	*unemployed*	0	*unemployed*	4
student	0	*student*	3.7	*student*	4
never worked	17.4	*never worked*	14.8	*never worked*	0

In order to avoid the problem of low frequencies (below 5) in a number of cells, the eight categories described above were collapsed into two categories either manual or non-manual occupations. Therefore, the chi-square analysis described in table 4.2.6 was calculated using a 2 x 3 table. The same procedure was used in calculating father's occupation, described in tables 4.2.7 and 4.2.8.

Table 4.2.6 :Mother's occupation (current or last paid position): chi square analysis

analysis	*value*	*df*	*significance*
Pearson Chi- Square	0.76	2	0.68

Table 4.2.7: Father's occupation (current or last paid position): group means

HSS		*PWS*		*stressed*	
occupation	*%*	*occupation*	*%*	*occupation*	*%*
intermediate/ managerial	20	*intermediate/ managerial*	0	*intermediate/ managerial*	0
skilled/ non-manual	13.3	*skilled/ non-manual*	34.8	*skilled/ non-manual*	17.6
skilled manual	26.7	*skilled manual*	43.5	*skilled manual*	41.2
partially skilled	26.7	*partially skilled*	8.7	*partially skilled*	17.6
unskilled	6.7	*unskilled*	13	*unskilled*	23.5
unemployed	0	*unemployed*	0	*unemployed*	0
student	0	*student*	0	*student*	0
never worked	0	*never worked*	0	*never worked*	0
not known	6.7	*not known*	0	*not known*	0

Table 4.2.8: Father's occupation (current or last paid position) : chi square analysis

analysis	*value*	*df*	*significance*
Pearson chi-square	1.55	2	0.46

4.2.2 Housing

Families described their housing in terms of the type and property status, whether mortgaged or rented accommodation. This is described in tables 4.2.9 to 4.2.12.

Table 4.2.9: Housing type : group means

HSS		*PWS*		*stressed*	
housing type	*%*	*housing type*	*%*	*housing type*	*%*
detached	16	*detached*	10	*detached*	0
semi-detached	24	*semi-detached*	40	*semi-detached*	25
terraced	40	*terraced*	40	*terraced*	52
flat	20	*flat*	10	*flat*	20

Table 4.2.10: Housing type: chi square analysis

analysis	*value*	*df*	*significance*
Pearson chi-square	7.07	6	0.31

The data in tables 4.2.9 and 4.2.10 show that, in each group, the largest proportion of families lived in terraced or semi-detached houses. A chi square analysis confirms that there are no significant differences between housing type and group status.

In order to identify non-independent cells within a significant chi-square, the contribution that each cell makes towards the final chi square value is calculated (see appendix 10) (A. Wade, Biostatistics Unit, ICH, personal communication). As we described below, each of the property status categories described separately in table 4.2.11 were collapsed into a dichotomous variable: either mortgaged, or rented (privately or from the council). Table 4.2.12 shows a significant chi-square value. More PWS families lived in mortgaged rather than rented accommodation as compared to the other two groups. This may be a reflection of the geographical distribution of the groups. Many HSS and stressed families lived in the greater London area (56% and 48% respectively) as compared to only 27 % of PWS families. The higher property prices in the greater London area may account for this difference, rather than it being as a result of a systematic difference in financial stability between the groups. There were no significant differences in terms of the number of bedrooms and living rooms, excluding kitchen and bathrooms, available to the family (tables 4.2.13 and 4.2.14). We also recorded the number of individuals living in the accommodation (tables 4.2.15 and 4.2.16).

Table 4.2.11: Property status: group means.

HSS		*PWS*		*stressed*	
property status	*%*	*property status*	*%*	*property status*	*%*
mortgage	24	*mortgage*	62	*mortgage*	25
council rental	60	*council rental*	38	*council rented*	63
private rental (furnished)	8	*private rental (furnished)*	0	*private rental (furnished)*	0
private rental (unfurnished)	4	*private rental (unfurnished)*	0	*private rental (unfurnished)*	12
tied to occupation	4	*tied to occupation*	0	*tied to occupation*	0

Table 4.2.12: Property status : chi square analysis

analysis	*value*	*df*	*significance*
Pearson Chi- Square	10.37	2	0.01

Table 4.2.13: Bedrooms and living rooms: group means

group	*n*	*mean*	*sd*
HSS	25	4.48	1.29
PWS	28	4.32	0.98
stressed	24	4.37	1.34

Table 4.2.14: Number of bedrooms and living rooms: ANOVA analysis

source	*df*	*ss*	*ms*	*F ratio*	*F probability*
between groups	2	0.34	0.17	0.12	0.89
within groups	74	107.97	1.46		
total	76	108.31			

Table 4.2.15: Number of individuals living in the accommodation: group means

group	*n*	*mean*	*sd*
HSS	25	5.68	2.11
PWS	30	4.00	1.25
stressed	24	4.9	1.83

Table 4.2.16: Number of individuals living in the accommodation: ANOVA analysis

source	*df*	*ss*	*ms*	*F ratio*	*F probability*
between groups	2	38.88	19.44	6.44	< 0.00
within groups	76	229.27	3.02		
total	78	268.15			

A post hoc Sheffe test, with a significance level of 0.05, revealed that the HSS families have significantly more individuals per household than PWS families. It is probable that this difference may be explained in part by the phenomenon known as 'stoppage' in which parents are less likely to have further children, after the birth of a child with a congenital condition, such as PWS. It is also possible that the PWS group have a smaller number of children simply because they are more likely to be intact, nuclear families. This is discussed further below.

Finally, we calculated the relative ratio of individuals to rooms giving a more accurate reflection of the accommodation available to each family (tables 4.2.17 and 4.2.18). This was calculated by dividing the number of rooms (living and bedrooms) by the number of individuals living in the accommodation. The greater the value, the greater living accommodation the family has. Given the non-significant differences between groups in terms of the number of rooms, but the significantly greater number of individuals in HSS families as compared to PWS households, it is unsurprising that there is a significant difference in the groups' room ratio. A post hoc Sheffe test at significance level 0.05, confirmed the difference in room ratio lay between the HSS and PWS groups.

Table 4.2.17: Room:person ratio. group means

group	n	mean	sd
HSS	25	0.86	0.28
PWS	30	1.16	0.47
stressed	24	0.96	0.33

Table 4.2.18: Room:person ratio: ANOVA analysis

source	df	ss	ms	F ratio	F probability
between groups	2	1.22	0.61	4.45	0.02
within groups	74	10.14	0.14		
total	76	11.36			

4.2.3 Care-giver Characteristics

Aspects of the analyses centre around parenting styles and so it was important to control for parental age which may influence parenting approach, in addition to other meaningful variables such as SES status. Parental ages are described in tables 4.2.19 and 4.2.20 below. The data show almost identical mean ages and distribution patterns in all groups. HSS group maternal ages ranged between 22 and 54 years, the PWS group between 24 and 48 years and the stressed group maternal age ranged from 29 to 54 years. Paternal ages ranged from 30 to 57 years, 29 to 58 years and 27 to 49 years respectively in each group.

Table 4.2.19: Parental age: group means

	HSS	n	PWS	n	stressed	n
mean mother age (sd)	34.57 (7.92)	21	34.15 (6.00)	26	37.80 (6.44)	20
mean father's age (sd)	39.36 (8.80)	14	38.77 (7.50)	22	37.53 (7.17)	15

Table 4.2.20: Parental age: ANOVA analyses

variable	source	df	ss	ms	F ratio	F Probability
mother's age	Between Groups	2	169.94	84.97	1.85	0.16
	Within Groups	64	2941.73	45.96		
	Total	66	3111.67			
father's age	Between Groups	2	25.70	12.85	0.21	0.81
	Within Groups	48	2906.81	60.56		
	Total	50	2932.51			

4.2.4. Family composition

Figure 4.2.1 describes the relatively high percentage of single parent families in all three groups as compared to the general population. Only 20% of families in the general population are headed by a single parent, though lower SES families are more likely to become single parents (Social Trends, 1996). With two exceptions (both of whom were in the PWS group), single parents were mothers rather than fathers. Table 4.2.21 illustrates that there were no systematic group differences in family type.

Figure 4.2.1: Family type (percentage)

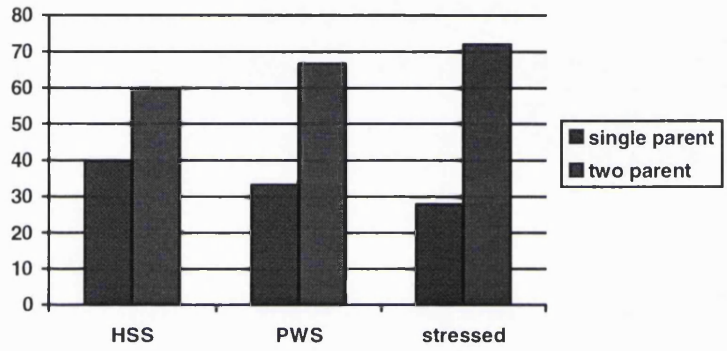
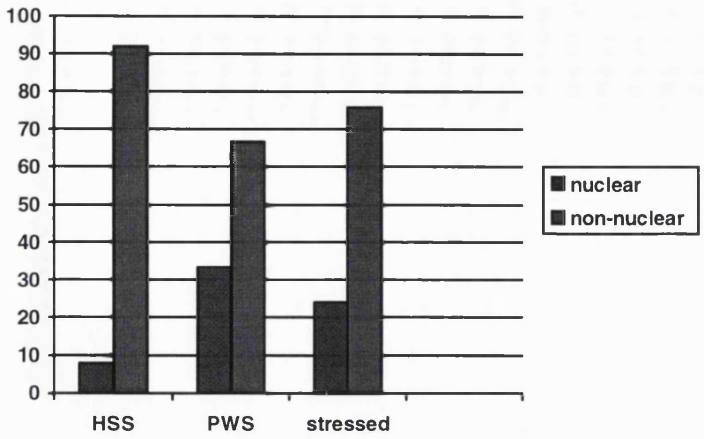


Table 4.2.21: Family type: chi-square analysis

analysis	*value*	*df*	*significance*
Pearson chi-square	0.81	2	0.67

Further, we recorded the proportion of 'intact' families. Our criteria for a nuclear family was that the index child lived with both their biological parents and full siblings. In other words, there had been no reconstitution within the family structure. This is described in figure 4.2.2.

Figure 4.2.2: Family structure (percentage)



We used a chi-square analysis (table 4.2.22) and inspection of the contribution that each cell made to the final chi square value (see appendix 10), we showed that the HSS group were considerably less likely to live in an intact, nuclear family as compared to the remaining groups. Though all three groups show proportionally more non-nuclear than nuclear families

Table 4.2.22: Family structure: chi-square analysis

analysis	*value*	*df*	*significance*
Pearson chi-square	18.01	2	> 0.00

3.2.4.1 Ordinal position

Figure 4.2.3 illustrates that the ordinal position of the index child in the PWS families was more likely to be first born, providing further evidence of stoppage in the PWS group. In table 4.2.23, we merged the rows in order to avoid small frequency counts, reducing the table to a 3 x 3 contingency table. First, second and third born and above were each of the 3 categories. By examining the contribution that each cell makes to the final chi square value (appendix 10), it is clear that children with PWS are more likely to be first born than either of the two groups.

Figure 4.2.3: Index child's ordinal position (actual frequency)

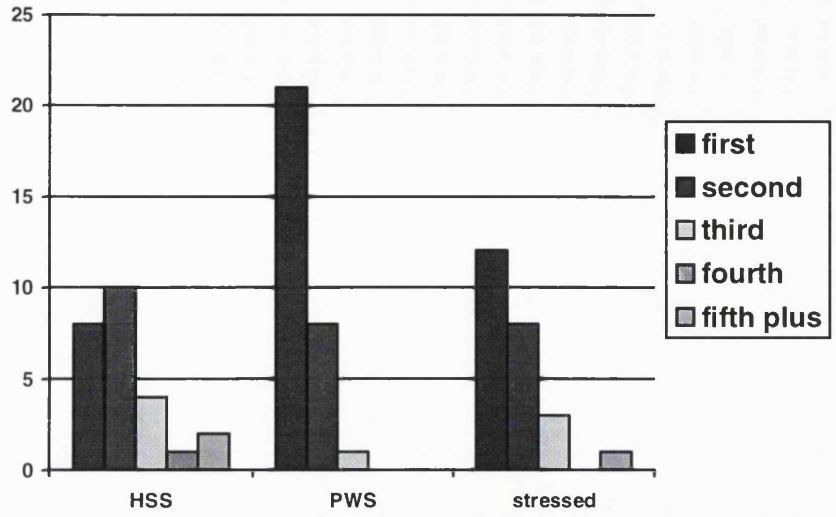


Table 4.2.23: Ordinal position: chi square analysis

analysis	*value*	*df*	*significance*
Pearson chi-square	10.24	4	0.04

4.2.5 Index child characteristics

4.2.5.1 Age and sex

Ages were calculated as decimal values, to ensure a precise comparison between groups. There was a decreasing age trend, for stressed children, HSS children and PWS children in the group order listed. However table 4.2.25 illustrates that this is a non-significant trend. Age ranged between 3.11 and 16.9 years, 5.58 and 15.29 years and 5.2 and 15.7 years in the HSS, PWS and stressed groups respectively. Similarly, there was an increasing proportion of girls in the stressed, HSS and PWS groups respectively, but this was not a significant difference (table 4.2.26).

Table 4.2.24: Index child's age and sex : group means

	HSS	*PWS*	*stressed*
mean age (sd)	9.04 (3.78)	8.75 (2.77)	10.61 (3.06)
sex (% female)	28%	33.3%	40%

Table 4.2.25: Index child's age: ANOVA analysis

source	*df*	*ss*	*ms*	*f ratio*	*f probability*
between groups	2	52.69	26.35	2.56	0.08
within groups	77	791.11	10.27		
total	79	843.80			

Table 4.2.26: Index child's sex: chi square analysis:

analysis	*value*	*df*	*significance*
Pearson chi-square	0.81	2	0.67

4.2.5.2 Racial group

We asked parents to describe their child's racial group. Figure 4.2.4 illustrates that all groups were predominately white. Previous HSS samples described at Great Ormond Street Hospital (Skuse, personal communication) have had similar racial characteristics. This may be due to referral bias. It was, of course, necessary to reflect this racial mix in the comparison groups. Accordingly, there were no significant group differences in racial group characteristics (table 4.2.27).

Figure 4.2.4: Index child's race (percentage)

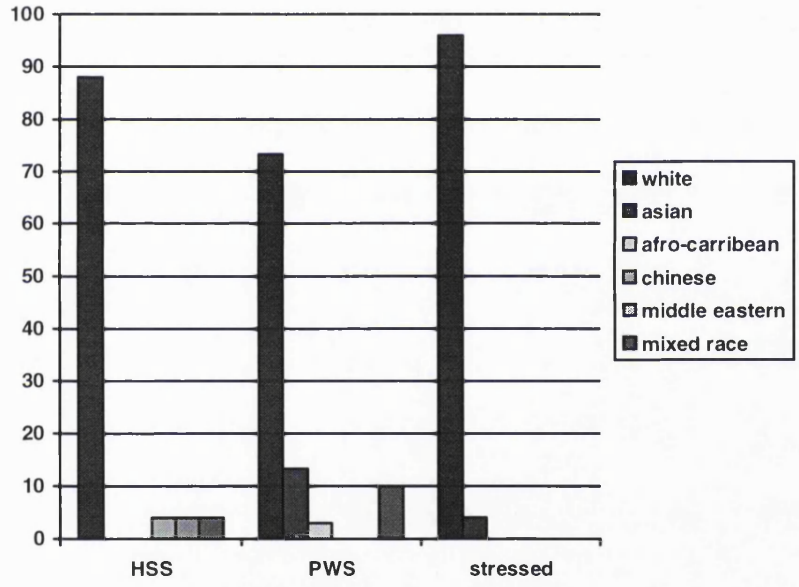


Table 4.2.27: Index child's race: chi square analysis

analysis	*value*	*df*	*significance*
Pearson chi-square	14.68	10	0.14

4.2.5.3 Child placement

Table 4.2.28: Placement of index child (percentage)

placement	*HSS (%)*	*PWS (%)*	*stressed (%)*
both natural parents	8	63.3	24
natural mother with father substitute	28	0	24
natural mother alone	32	23.3	24
natural father with substitute mother	8	3.3	4
natural father alone	0	6.7	0
other relatives	0	3.3	8
foster carers	24	0	12
adopted	0	0	4

As described in table 4.2.22, HSS affected children were significantly less likely to live with both biological parents than were the other two groups. Note also that none of the children with PWS were living in adoptive or foster placements. One stressed child lived with her maternal aunt and uncle, another with his maternal grandparents. One PWS child lived with his father and paternal grandmother and another lived with his paternal aunt and uncle. As noted above, these relatives are described as the child's 'parents' for demographic purposes only.

3.2.6 Sibling characteristics

3.2.6.1 Age and sex

Table 4.2.29 describes the age and sex characteristics of the full siblings in each group. There were no significant differences between the groups in terms of sex (Pearson chi square value = 1.51, df = 2, p = 0.47) or age (F =1.95, p = 0.15). Table 4.2.30 describes the same characteristics for the half and unrelated siblings in each group. There were no significant sex (Pearson chi square value = 2.81, df =1, p = 0.09) or age (F =2.93 , p = 0.10) differences between the groups.

Table 4.2.29: Full siblings age and sex : group means

	HSS full siblings (n=30)	*PWS full siblings (n = 29)*	*stressed full siblings (n = 19)*
mean age (sd)	10.05 (3.49)	8.43 (4.08)	10.35 (3.43)
sex (% female)	54%	41%	37%

Table 4.2.30 :Half or unrelated siblings age and sex: group means

	HSS half or unrelated siblings (n=14)	*PWS half or unrelated siblings (n = 0)*	*stressed half or unrelated siblings (n = 9)*
mean age (sd)	6.63 (3.91)	n/a	8.62 (4.37)
sex (% female)	78%	n/a	45%

4.3 Section A: Stress, parenting style and family environment

4.3.1 Psychosocial Adversity

***Hypothesis**: The children affected with HSS are living in conditions of psychosocial adversity, comparable to the stressed group but distinct from the PWS group.*

This hypothesis is extremely difficult to test in a precise manner. By definition, the stressed group were selected from severely stressed family environments. 15 (60%) of these families were referred to social services due to concerns about the quality of parenting that the children were receiving. For 10 stressed children referred to the study through the EBD schools, the precise nature of the intra-familial stress was not disclosed but became apparent following the assessment. Table 4.3.1.1 describes the nature of concerns in the stressed group.

In contrast children affected with HSS were not ascertained through social services agencies. The HSS group were recruited, consecutively, only according to the diagnostic algorithm. There was no pre-selection made on the basis of children's stressful circumstances. Despite this, 68% of HSS families had social services involvement (table 4.3.1.2). Significantly more children in the stressed group had social services involvement (100%) than in the HSS group (Pearson value = 9.52, p <0.00). However given that the stressed group were recruited precisely on that basis this is hardly surprising. It is noteworthy that only 4% of the general population have social services involvement of this kind (Skuse and Bentovim, 1994).

With one exception, HSS social service referral concern surrounded the parenting that the index child was receiving. The HSS exception (LR) involved the index child's older sibling who had requested to be put into care and had made allegations against her mother and step father, which were not substantiated. Therefore there were no documented concerns, according to the care-giver, about LR specifically. In the remaining 7 HSS cases, at the time of assessment, 6 families were identified by professionals as having psychosocial difficulties in terms of the quality of parenting and emotional environment provided by care-givers. Professionals who reported concerns included health-visitors, psychiatrists, head teachers, speech-therapists and General Practitioners. The final case (AS) was a child who had been living in

the Lebanon during civil war bombing. The family had subsequently emigrated approximately 10 times, in a period of 5 years, to countries in Europe and North Africa. We were not aware of any other agencies' concerns about parenting specifically in this case - though the child's circumstances may certainly be regarded as stressful.

Table 4.3.1.1: Categories of chronic stress (stressed group only)+

	cases on whom full details were available (social services and GOSH records)			
case	*physical abuse*	*emotional abuse*	*sexual abuse*	*neglect*
JC				✓
GL	✓			
GA				✓
RB		✓		
TA				✓
PB				✓
DS	✓	✓		
LR			✓	
CH	✓	✓		
MW				✓
HE			✓	
AM	?	?		
SH	✓	✓		
SS		✓		
VS			✓	
	*cases recruited from EBD schools**			
case	*physical abuse*	*emotional abuse*	*sexual abuse*	*neglect*
JP	✓	✓		
TJ		✓	?	
NM		✓		
BF				?
GP				?
CJ		✓		
NB				✓
EB	✓	✓		
RG		?		
NS	✓	✓		

** these classifications were made on the basis of parental information about their involvement with social services and after consultation with Professor Skuse, Consultant Psychiatrist*

+ ? indicates abuse is suspected, not confirmed

Table 4.3.1.2: Categories of chronic stress (HSS group only) +

case	*Social services involvement*	*physical abuse*	*emotional abuse*	*sexual abuse*	*neglect*
JC	✓		➳		➳
DS	➳	➳	➳		➳
VN	➳	➳	➳	?	
BD	➳				?
CT	➳		➳		
KN	➳		➳		
HW			?		
BB	➳		➳		
CO	➳	➳	➳		
SB	➳		?	➳	
AW			?		
TO			?		
MKC	➳	?	➳		
SD					?
LR	➳				
AH			?		
LS	➳		➳		➳
GA	➳		?		
JS	➳				➳
AP					?
AS					
KC	➳		➳	➳	
KF	➳				➳
CH			?		
MB	➳				➳

+ ? indicates that abuse is suspected, not confirmed.

In the PWS group, one family had social services involvement surrounding psychosocial issues. In this case, the index child's mother reported ' he hates me and I hate him', and made further similar comments in his presence that may amount to a suspicion of emotional abuse. Social services were arranging, at the time of assessment, that this child be placed in a residential school. Social workers did work with a number of other families in the PWS group, in order to arrange transport to school and so on.

Removal from home

Seven children in the HSS group were removed from home subsequent to the assessment, voluntarily at the request of social services, or by Care Order. Four children in the stressed group were also removed from home under these circumstances, though in one case the child has been returned home. The

percentage of children removed from home in the stressed as compared to the HSS group (children with PWS were excluded) was not significantly different (Pearson chi square value = 1.05, df = 1, p = 0.30).

Type of abuse or stress experienced

In order to explore qualitatively the type of stress experienced or *suspected,* only the HSS and stressed children were compared. The PWS group were not included in these analyses. (table 4.3.1.3)

Table 4.3.1.3: Type of stress experienced/suspected: chi-square analyses (HSS and stressed groups only compared.)

variable	*value*	*df*	*significance*
physical abuse	2.60	1	0.11
sexual abuse	0.16	1	0.68
emotional abuse	2.05	1	0.15
neglect	0.35	1	0.56

Punishment (parental report)

Parents were asked in the HSSDI to describe the type of reprimand and punishments that they used with their children. Care-givers reported the severity of behaviour demonstrated by their children in many cases to be comparable across groups (see 4.4.8 to 4.4.12). This indicates that degree of reported behavioural disturbance in the groups would not confound the comparison. We compared the frequency of frankly abusive punishments reported within each group. The definition of an abusive punishment included: being hit with an implement, being locked in a room for a substantial period of time, or punishments which might be viewed as emotionally damaging such as a care-giver destroying a favourite toy belonging to the child. 28% of the HSS, 3.3% of PWS and 20% of the stressed care-givers described using punishment fitting this criteria. The chi square comparison was significant (Pearson value = 6.47, df = 2, p = 0.04). By examining the contribution that each cell made to the final chi square value (appendix 10), it is clear that the PWS group are significantly less likely to use abusive punishments than either the HSS or PWS groups. After subtracting the contribution that the PWS group made to the chi square, leaving 1.56, the chi square at an alpha of 0.05 (df=1) was no longer significant. This indicates that the HSS and stressed group care-givers reported using abusive punishments with comparable frequency.

4.3.1.1 Summary

Although the hypothesis is rather difficult to test accurately, within the limitations of the data, it is supported. The stressed group were, by definition, involved with social services. Despite independent recruitment procedures, almost 70% of the HSS group families had social services involvement too, as compared to 4% in the general population (Skuse and Bentovim, 1994). There was no significant difference in the type of abuse described or suspected in either the HSS or stressed groups. Further, according to care-givers' report, HSS and stressed children were reprimanded in an abusive manner with comparable frequency.

4.3.2 Expressed Emotion (Vaughn and Leff, 1976b)

The data produced from the Expressed Emotion (EE) scales were analysed in a number of ways. Three of the sub-scales are used to make the classification of high or low EE: critical comments, hostility and emotional over-involvement (EOI). The two remaining categories, positive comments and warmth, were examined separately but are not used in the EE classification system. Each sub-scale was analysed separately in order to develop a more detailed profile of the quality of the 'emotional temperature' surrounding the index children. In view of this hypothesis, the foster family, in which an affected HSS child was recovering, was not included in these analyses.

There is no evidence in the literature to suggest that IQ influences the ratings of EE but as there is a systematic difference in IQ between groups (see 4.4.1), it was considered appropriate to covary cognitive ability in all analyses. In each case post hoc tests were performed on group means with IQ regressed out, an equivalent procedure to covarying IQ in the ANOVA analyses.

4.3.2.1 Critical comments

***Hypothesis**: There will significantly more critical comments in the HSS and stressed families as opposed to the PWS group.*

Table 4.3.2.1 describes the group means for critical comments, and though there is a trend in the predicted direction, table 4.3.2.2 shows that the difference is not significant. The hypothesis is not supported.

Table 4.3.2.1: Expressed Emotion sub-scales: group means

sub-scale	*HSS (n = 24) mean (sd)*	*PWS (n = 30) mean (sd)*	*stressed (n= 24) mean (sd)*
*critical comments**	5.04 (3.86)	3.03 (3.04)	5.21 (4.19)
*food related critical comments**	2.40(2.55)	1.35 (2.04)	0.76 (1.34)
hostility+	0.46 (0.98)	0.17 (0.65)	0.46 (0.83)
Emotional overinvolvement+	1.04 (1.27)	0.70 (0.95)	0.48 (0.73)
*positive remarks**	1.71 (1.49)	2.00 (1.39)	2.26 (2.26)
warmth+	2.08 (1.44)	3.37 (1.10)	2.83 (1.13)

** frequency counts*
+ global ratings

Table 4.3.2.2: Critical comments and positive remarks: ANOVA analyses

variable	*F (df =2)*	*p*
critical comments	2.63	0.08
food related critical comments	3.95	0.02
positive remarks	1.51	0.23

4.3.2.2 Food related critical comments

Hypothesis: *Of the critical comments made, a significantly greater proportion will be food related in the HSS group as compared with the PWS group*

Critical comments were classified in terms of their content, whether food related or not. The category was applied widely. Examples of food related comments include: ' She'll rip it (food) out the packet. It's not as if she's got the sense, like some would, to use a knife...' or ' He's destructive with food...I wouldn't mind if just sat there ...and ate it, but he takes them apart' or 'Nine times out of ten he can't be bloody hungry. Why he needs it or why he wants it is a complete mystery... he can't be hungry but G says he is hungry'. Food related comments were analysed in two ways: absolute number of food related comments and food related critical comments as a proportion of the total number of critical comments. There was a significant group difference in the absolute number of food related comments but using a Sheffe post hoc analysis, this simply showed that the stressed care-givers made fewer food related critical comments than the HSS care-givers. When food related comments are analysed as a proportion of the total number of critical comments made, both the HSS and the PWS group care-givers made a significantly greater proportion of food related critical comments than the stressed group ($F = 8.34$, $p < 0.00$). In fact, PWS care-givers tended to make proportionately more food related critical comments (52%) than the HSS group (32%). If only those families who are high EE are included in the analysis, this trend is maintained. 58% of the critical comments made were food related in the high EE PWS group and 42% in the High EE HSS group. The proportion of food related critical comments remained unchanged whether the full stressed group or only those with High EE were included (13% and 14% respectively).

The analyses do not support the hypothesis, as analysing either the absolute number of food related critical comments or as a proportion of total critical comments, shows that there are no significant differences between the HSS and PWS groups.

4.3.2.3 Hostility

***Hypothesis**: Ratings of hostility will be higher in the stressed and HSS groups as compared to the PWS groups.*

Hostility is rated on a scale of 0 to 3, with ratings of 1 and above being relatively unusual in this sample. Vostanis and Nicholls (1992) note that none of the parents in a non-referred group scored above 0. It is questionable whether there is equal distance between the ratings. It was considered most appropriate to treat this variable as ordinal, and therefore non-parametric statistics were applied.

Figure 4.3.2.1 describes the Hostility ratings for the groups. A rating of 1 or above on hostility is indicative of high EE. 97% of the PWS families expressed no hostility, as compared to 79% of the HSS group care-givers and 71% of the stressed children's care givers . A Pearson Chi-square analysis showed that this was not a significant group difference (Pearson value 4.78, df = 2, p = 0.09).

The rating scale is as follows:

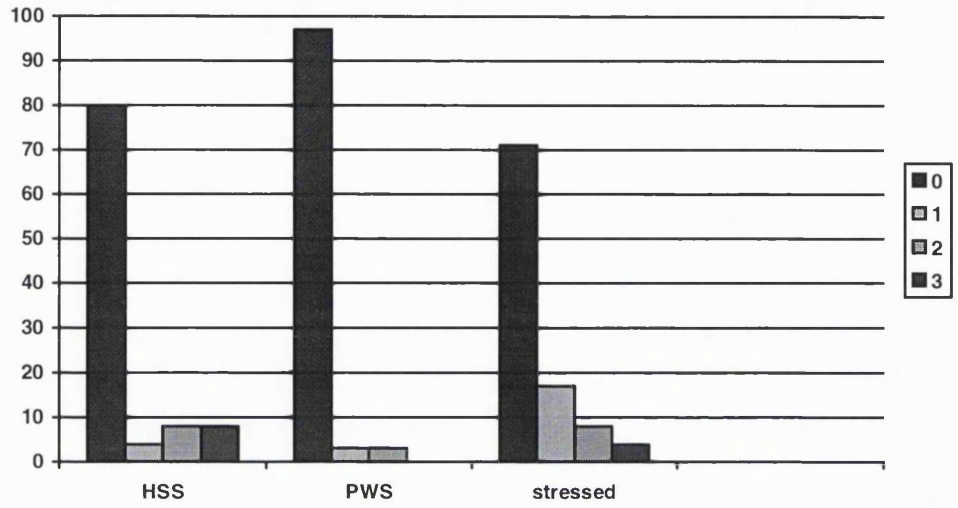
0: No hostility

1: Generalized hostility (dislike for the person, not just the persons' behaviour). For example: 'It's horrible having K around the house".

2: Rejection hostility: (a more direct form of frank dislike) For example: 'You just wish she could go on holiday and never come back'

3: Generalized and rejection hostility. This means that both types of hostility are expressed by the care-giver.

Figure 4.3.2.1: Ratings of hostility (0-3) by group.



The hostility data were also analysed using a non-parametric Kruskal-Wallis one way ANOVA, allowing all four categories to be analysed. Mean ranks were 40.90, 35.28 and 43.38 for the HSS, PWS and stressed group respectively. The chi square (4.09, df = 2) was not significant (p = 0.13).

4.3.2.4 Emotional over-involvement

***Hypothesis**: There will be higher ratings of Emotional Over-involvement (EOI) in the stressed and HSS groups as compared to the PWS group.*

This scale reflects care-givers' self-sacrificing attitudes and inappropriate guilt. It has been described as a similar concept to 'enmeshment' (EE training manual). As described above, this scale was treated as an ordinal scale, as it is debatable whether there are equal intervals between each point. A Kruskal-Wallis ANOVA showed that there was no significant group difference in terms of EOI. (chi-square = 2.49, df = 2, p = 0.29). Interestingly there was a non-significant trend for the HSS group to show a greater level of EOI (mean rank 43.77) than the PWS (mean rank 38.60) or stressed group (34.54). The hypothesis was not supported.

4.3.2.5 Positive comments

Hypothesis: *The PWS group will make significantly more positive comments than either the stressed or the HSS groups.*

As described in table 4.3.2.2, there was no significant group difference in terms of positive comments. There was a trend, against the predicted direction, for the HSS caregivers to use fewer positive comments in describing the index children than the PWS group, who in turn used fewer positive comments than the stressed group.

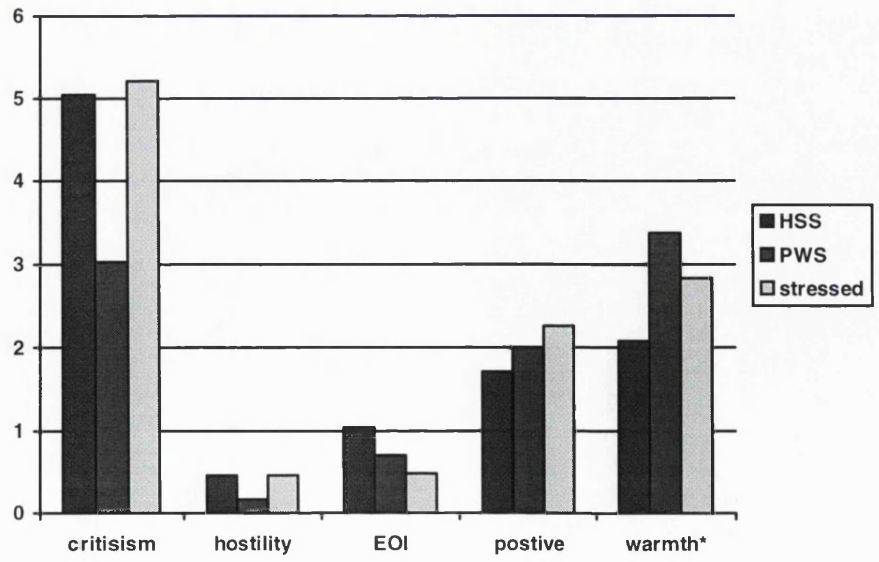
4.3.2.6 Warmth

Hypothesis: *The stressed and HSS groups will have significantly lower warmth ratings in comparison to the PWS group.*

Warmth was treated as an interval scale, with normal distribution and equal interval between each point. There was a significant group difference ($F = 7.40$, $p < 0.00$). Post-hoc tests (Sheffe at $p = 0.05$) showed that the HSS group were significantly colder towards the index child than either the stressed or the PWS groups. The hypothesis was partly supported, as HSS group care-givers were rated as significantly colder than either of the other groups.

In summary, Figure 4.3.2.2 illustrates the sub-scale profiles for each group.

Figure 4.3.2.2: EE sub-scales means by group



* significant group difference at $p < 0.05$

4.3.2.7 Sub-scale correlations

In order to describe the relationship each EE scale has with one another, correlation coefficients were calculated. Further, using parental report of the severity of hyperphagia (see 4.4.6), the relationship of each sub-scale with reported appetite disturbance was explored. The higher the value of the hyperphagia variable, the more severe the reported hyperphagic behaviour.

Table 4.3.2.3 illustrates the correlation coefficients across the full sample. The pattern between sub-scales is, as one may have predicted, with critical remarks and hostility having positive significant correlations . However it should be noted that the scales are orthogonal in theory (EE training manual). Reported hyperphagia is positively correlated ($p < 0.00$) with food related critical comments. This suggests that care-givers comment negatively about food related issues more frequently as the severity of reported behaviour increases. However, the frequency of general critical comments is unrelated to the severity of hyperphagic behaviour. When care-giver reported behavioural disturbance, *excluding* hyperphagia[1] is correlated with non-food critical comments, the relationship is not significant ($r = 0.17$, $p = 0.17$). In other words, the severity of behavioural disturbance does not influence the frequency of critical comments in non-food related behaviour but there *is* a relationship between reported severity and critical comments in hyperphagic behaviour. It may be that hyperphagia is a relatively difficult behaviour for care-givers to accept. There is no evidence in the literature to suggest that the severity of disturbance should influence the rating of high or low EE (Vaughn and Leff 1976b). Though other studies have found significant relationships between individual scales and the severity of behaviour (Vostanis, Nicholls and Harrington,1994).

However the pattern of correlations differed within groups (see tables 4.3.2.4-6). The HSS and PWS groups did not, in fact, show a significant relationship between reported hyperphagia and food related critical comments, while the stressed group care-givers did. The stressed group, as described above made significantly less food related critical comments overall. Across the small range, therefore, there seems to be a sensitive relationship in the stressed group. Further there was a significant indirect relationship between reported hyperphagia and warmth in the stressed group only. The non-significant correlation between non-food critical comments and non-hyperphagic

[1] this variable is the summed score of all the non-hyperphagic behavioural disturbance variables in the HSSDI.

behavioural disturbance held across all groups (r = 0.27, p = 0.25 (HSS), r = 0.22, p = 0.28 (PWS) and r = 0.27 p = 0.24 (stressed)).

Table 4.3.2.3: Expressed Emotion sub-scale correlations: full sample

sub-scale	*full sample*						
	critical comments	*food critical comments*	*hostility*	*EOI*	*positive remarks*	*warmth*	*hyperphagia reported*
critical comments	*	r = 0.64 p < 0.00	r = - 0.50 p < 0.00	r = 0.38 p < 0.00	r = -0.07 p = 0.54	r = - 0.50 p < 0.00	r = 0.16 p = 1.67
food critical comments	*	*	r = 0.34 p < 0.00	r = 0.43 p < 0.00	r = 0.08 p = 0.47	r = -0.44 p < 0.00	r = 0.42 p < 0.00
hostility	*	*	*	r = 0.17 p = 0.13	r = -0.10 p = 0.36	r = -0.44 p < 0.00	r = 0.06 p = 0.61
EOI	*	*	*	*	r = 0.05 p = 0.64	r = -0.12 p = 0.32	r = 0.15 p = 0.20
positive remarks	*	*	*	*	*	r = 0.45 p < 0.00	r = -0.14 p = 0.22
warmth	*	*	*	*	*	*	r = -0.17 p = 0.13
hyperphagia reported	*	*	*	*	*	*	*

Table 4.3.2.4: Expressed Emotion sub-scale correlations: HSS group

sub-scale	*HSS*						
	critical comments	*food critical comments*	*hostility*	*EOI*	*positive remarks*	*warmth*	*hyperphagia reported*
critical comments	*	r = 0.45 p = 0.11	r = 0.56 p < 0.00	r = 0.27 p = 0.21	r = - 0.20 p = 0.34	r = -0.71 p < 0.00	r = 0.30 p = 0.15
food critical comments	*	*	r = 0.57 p = 0.01	r = 0.36 p = 0.12	r = -0.24 p = 0.31	r = -0.64 p < 0.00	r = 0.25 p = 0.29
hostility	*	*	*	r = 0.26 p = 0.21	r = -0.05 p = 0.80	r = - 0.53 p = 0.01	r = 0.05 p = 0.80
EOI	*	*	*	*	r = 0.70 p = 0.73	r = - 0.10 p = 0.65	r = 0.13 p = 0.53
positive remarks	*	*	*	*	*	r = 0.64 p < 0.00	r = -0.21 p = 0.32
warmth	*	*	*	*	*	*	r = -0.19 p = 0.36
hyperphagia reported	*	*	*	*	*	*	*

Table 4.3.2.5: Expressed Emotion sub-scale correlations: PWS group

sub-scale	*PWS*						
	critical comments	*food critical comments*	*hostility*	*EOI*	*positive remarks*	*warmth*	*hyperphagia reported*
critical comments	*	r = -0.12 p = 0.77	r = 0.15 p = 0.42	r = 0.40 p = 0.03	r = 0.28 p = 0.14	r = - 0.34 p = 0.06	r = 0.41 p = 0.03
food critical comments	*	*	r = 0.12 p = 0.56	r = 0.48 p = 0.01	p = 0.35 p = 0.08	r = - 0.24 p = 0.25	r = 0.34 p = 0.09
hostility	*	*	*	r = -0.08 p = 0.66	r = -0.04 p = 0.84	r = -0.57 p < 0.00	r = 0.12 p = 0.53
EOI	*	*	*	*	r = 0.32 p = 0.09	r = 0.01 p = 0.96	r = -0.05 p = 0.80
positive remarks	*	*	*	*	*	r = 0.31 p = 0.09	r = 0.06 p = 0.77
warmth	*	*	*	*	*	*	r = -0.04 p = 0.85
hyperphagia reported	*	*	*	*	*	*	*

Table 4.3.2.6: Expressed Emotion sub-scale correlations: stressed group

sub-scale	*stressed*						
	critical comments	*food critical comments*	*hostility*	*EOI*	*positive remarks*	*warmth*	*hyperphagia reported*
critical comments	*	r = 0.40 p = 0.07	r = 0.63 p < 0.00	r = 0.52 p = 0.01	r = -0.20 p = 0.36	r = - 0.30 p = 0.15	r = 0.32 p = 0.13
food critical comments	*	*	r = 0.28 p = 0.21	r = 0.21 p = 0.36	r = 0.24 p = 0.29	r = -0.20 p = 0.39	r = 0.67 p < 0.00
hostility	*	*	*	r = 0.32 p = 0.10	r = -0.19 p = 0.36	r = -0.10 p = 0.64	r = 0.33 p = 0.01
EOI	*	*	*	*		r = -0.11 p = 0.61	r = -0.06 p = 0.77
positive remarks	*	*	*	*	*	r = 0.62 p < 0.00	r = -0.15 p = 0.50
warmth	*	*	*	*	*	*	r = -0.41 p = 0.05
hyperphagia reported	*	*	*	*	*	*	*

4.3.2.8 High or low EE

Hypothesis: *HSS and stressed families will show high Expressed Emotion significantly more often than the PWS families*

Although each of the scales individually provides a description of the quality of emotional response the index children are receiving, intra-familial stress is most reliably and validly measured by the Expressed Emotion variable. It is a dichotomous variable and care-givers are described as either high or low EE. The defined criteria for high EE is described in the method section (3.2.7). As described in table 4.3.2.7, there is a significant group difference. By examining the contribution that each cell makes towards the final chi-square value (see appendix 10), it is evident that the PWS group families are significantly less likely to show high EE (23%) as compared to the HSS group care-givers (50%) and the stressed group (54%). Further when the PWS group's chi-square contribution is subtracted from the final chi-square value, the remainder is not significant (df =1, at p = 0.05).

Table 4.3.2.7: Pearson chi-square analysis: high Expressed Emotion by group

chi-square	value	df	p
Pearson	6.39	2	0.04

4.3.2.9 Summary:

The hypotheses are partly supported by the analyses. In examining each individual sub-scale, only the warmth scale showed any significant group difference, with HSS care-givers expressing less warmth than either of the other groups. The stressed care-givers also expressed less criticism concerning food. All other sub-scale comparisons were insignificant.

The hypothesis that both stressed and HSS care-givers were more likely to be high EE than the PWS group was supported, indicating a higher level of intra-familial stress in the stressed and HSS groups as compared to the PWS group.

4.3.3 Family Environment Scale (Moos and Moos,1986)

4.3.3.1 Group profiles

***Hypothesis**: The HSS and stressed group will show significantly higher conflict, and control scores but significantly lower scores on the cohesion, expressiveness, independence and intellectual and recreational activities sub-scales as compared to the PWS group families. In sum PWS families provide a family environment profile comparable to the Family Environment Scale (FES) normative group while the stressed and HSS families report a family environment score profile similar to the FES 'distressed group'.*

The Family Environment Scale (FES, Moos and Moos, 1986) assesses the family ethos on a number of scales. In this section we were assessing family environment, with reference to the groups, therefore one foster family who was providing a 'recovery environment' was excluded from these analyses.

The FES provides 10 sub scales. The standard score group means for each of these are reported in table 4.3.3.1. The mean T score based on the FES normative sample is 50. A T score of 60 or more is considered 'elevated' (Moos and Moos,1986).

In each sub-scale, the means show trends in the predicted direction though these are not invariably significant. A series of ANOVA analyses was performed on each of the sub-scales, with group as the only factor. These analyses are described in table 4.3.3.2. Cohesion showed a significant group effect ($F = 13.18$, $p < 0.000$), with means of 50.28 (sd 13.67), 59.34 (sd 7.54) and 40.88 (sd 15.80) for the HSS, PWS and stressed groups respectively. Post hoc Sheffe tests showed that, at an alpha of 0.05, the stressed group were significantly less cohesive than the PWS group, but was not significantly different from the HSS group. Expressiveness showed a significant group effect (with $F = 8.89$, $p = <0.000$) . Post hoc analysis showed that at an alpha of 0.05, as before the stressed group were significantly less expressive than the PWS but not significantly different from the HSS group families. Further the active/recreational orientation scale revealed significant group effects ($F = 4.75$, $p = 0.01$) but in this case post hoc testing showed that none of the groups were significantly different from one another (see table 4.3.3.1). As hypothesised there was a significant group effect in family conflict ($F = 3.36$ $p = 0.04$) in the predicted direction with stressed families having significantly greater conflict than the PWS families. However, the HSS and PWS families groups were not significantly different from one another. Table 4.3.3.2 also shows a significant group effect for

control. Sheffe post hoc analysis (at the 0.05 level) indicates that the stressed families demonstrated significantly higher control than the PWS group but were not significantly different from the HSS group families (table 4.3.3.1). This sub-scale indicates the extent to which rules and procedures are used in the family, a high score is indicative of an authoritarian parenting style (Ollendick, Laberteux and Horne, 1978). There was a non-significant trend for stressed and HSS families to score higher on achievement orientation, (see tables 4.3.3.1 and 4.3.3.2), a sub-scale also predictive of authoritarian parenting style.

Table 4.3.3 1 : FES sub-scales: group means

FES scale	*HSS (n= 14) mean (sd)*	*PWS (n= 29) mean (sd)*	*stressed (n = 17) mean (sd)*
cohesion	50.28 (13.67)	59.34 (7.54)	40.88 (15.80)
expressiveness	51.28 (12.13)	55.57 (11.06)	40.47 (12.38)
conflict	51.00 (13.68)	47.79 (10.77)	56.70 (9.81)
independence	39.86 (14.66)	47.14 (12.78)	41.23 (14.52)
achievement orientation	42.93 (11.96)	39.59 (12.20)	45.70 (9.76)
intellectual/cultural orientation	42.78 (11.72)	46.21 (12.16)	39.41 (11.94)
active/recreational orientation	42.21 (9.46)	51.52 (11.95)	42.59 (11.94)
moral/religious emphasis	42.07 (5.25)	46.55 (10.47)	41.88 (7.95)
organisation	44.78 (10.48)	50.41 (11.60)	49.29 (11.88)
control	49.21 (9.82)	48.41 (8.86)	56.82 (10.04)

Table 4.3.3.2: FES sub-scales: ANOVA analyses

variable	*F (df = 2)*	*p*
cohesion	13.18	< 0.000
expressiveness	8.89	< 0.000
conflict	3.36	0.04
independence	1.73	0.18
achievement orientation	1.56	0.22
intellectual/cultural orientation	1.75	0.18
active/recreational orientation	4.75	0.01
moral/religious emphasis	2.02	0.14
organisation	1.17	0.32
control	4.59	0.01

4.3.2.2 Individual families

FES family type classification:

Using the FES classification system (Moos and Moos, 1986), both the stressed and the HSS families are classified as disorganised because their mean score falls below 50 on the organization scale. The PWS families narrowly miss the support orientated family classification. The criteria for this category is a score of cohesion or expressiveness of 60, (the PWS families' mean is 59.34 on cohesion) or more and either cohesion or expressiveness being larger than the conflict score. They do not fall into any other category.

Examining the families classifications individually, within the groups shows that 6 % of the HSS families, 21 % of the PWS and 5% of the stressed families were classed as independence orientated. This category is defined as scoring above 60 on the independence scale and scoring lower on the achievement, intellectual-cultural and moral/religious scales than the independence scale. Achievement orientated families are those who have an achievement score of 60 or more, and intellectual/cultural and moral/religious sub-scales lower than the achievement sub-scale scores. 4% of the HSS 10% of the PWS and 19% of the stressed families fell into this category. The moral-religious family type (moral/religious score of above 60, and intellectual-cultural score above the moral/religious score) described only 1 (3%) PWS group family and none of HSS or stressed families.

6 % of the HSS families and 17 % of the PWS families were classified as intellectual/culturally orientated. None of the stressed families fell into this category. Families classified in this way have a intellectual/cultural score of over 60. 35%, 48% and 5 % of the HSS, PWS and stressed groups respectively fell into the support orientated category, defined with a score of 60 or more on the cohesion or expressiveness scale and a score in either these two scales that exceeds the score on the conflict scale. Conflict orientated families are those who score over 60 on that sub-scale. This applied to 23% of case families, 14% of PWS group families and 37% of the stressed families. Disorganised families (defined above) described 48% of the HSS and PWS families and 45 % of stressed families. A series of Pearson chi square analyses showed that only the support orientated classification was significantly different between the groups (Pearson value 9.80, df =2, $p > 0.00$). By examining the relative contribution each cell made to the final chi square score (appendix 10), it was clear that the stressed group were significantly less likely to be support orientated than either the PWS or HSS

groups. When the contribution of the stressed group is subtracted from the total chi-square value, the value was insignificant at 0.05 (df = 1). All other comparisons were insignificant.

4.3.2.3 Summary

The analyses described partly supports the hypotheses. Using the FES classification system, the stressed and HSS families were more similar to one another as they were identified as disorganised, while the PWS families' profile indicated a support orientated family environment . In cohesion, expression, conflict and control, the stressed families profiles were significantly different from the PWS group but not significantly distinct from the HSS group families. Further the HSS group families were not distinct from the PWS families on these sub-scales. In other words, the HSS families were between the other two groups in terms of family environment, with the stressed and PWS group at either extreme. Against the hypothesis, stressed families were significantly less likely than both PWS and HSS families to be classified as support orientated.

4.3.4 Physiological stress reactivity (salivary cortisol)

***Hypothesis**: the HSS and stressed groups will show a characteristic Hypothalamic-pituitary-adrenal (HPA) response to acute exercise stress in comparison to the PWS and normal comparison groups.*

There are wide inter-individual variations in baseline cortisol levels (Kiess et al, 1995) which could confound detection of group specific differences. The aim in this analysis was to describe the patterns of HPA *reaction and recovery* following an acute stressor when chronically stressed children are compared to those who are not. HPA axis activity was measured using salivary cortisol levels. It was hypothesised that the HSS and stressed children would show similar HPA axis reactions, distinct from that of the PWS children, as PWS is not commonly associated with stress. However there is a potentially confounding factor within this comparison. Obesity, often described in PWS, elevates cortisol in plasma and saliva, therefore it was considered necessary to include a normal comparison group in the analyses. In order to explore possible group specific baseline cortisol levels, a one-way ANOVA was performed with the pre-test cortisol sample means. There was no significant group difference in the baseline salivary cortisol measure ($F = 0.65$, $p = 0.58$, $df = 3$). Table 4.3.4.1 describes the cortisol levels for the groups pre-test and for each of the 4 samples taken 10, 20, 30 and 60 minutes after the exercise stress. There was a wide distribution of cortisol levels within each sample, illustrated by the large standard deviations. This is particularly noticeable in the stressed and PWS groups. The test was administered in early afternoon, when cortisol levels are falling according to the circadian rhythm.

Table 4.3.4.1: Salivary cortisol measures:group means

saliva sample	*HSS (n= 24) mean (sd)*	*PWS (n=26) mean (sd)*	*stressed (n=24) mean (sd)*	*comparison (n=20) mean (sd)*
pre-test	8. 28 (8.93)	10.51 (10.81)	11.80 (20.03)	6.69 (4.16)
sample 2	8.79 (7.76)	15.30 (20.36)	11 91 (20.61)	6.40 (5.19)
sample 3	9.43 (7.60)	15.86 (20.69)	11.23 (19.37)	7.30 (6.73)
sample 4	7.69 (7.13)	15.03 (20.14)	11.37 (20.14)	7.91 (6.74)
sample 5	8.78 (5.96)	12.48 (12.85)	8.07 (7.09)	6.60 (6.36)

Group mean pulse rates for the groups at baseline were 95.91 beats per minute (bpm) (sd 15.74), 92.85 bpm (sd 15.10) and 84.50 bpm (sd 16.67) for the HSS, PWS and stressed groups respectively. Pulse rate data were not available for the normal comparison children as the exercise stressor was administered to all 20 children simultaneously. An ANOVA analyses showed that there was no significant group effect ($F = 2.93$, $p = 0.06$, $df = 2$). Immediately after the exercise stress, pulse rates were almost identical across the groups. 161.26 bpm (sd 21.26) in the HSS group, 161.12 bpm (sd 17.90) in the PWS group and 160.08 bpm (sd 19.08) in the stressed group. A repeated measures ANOVA, with pulse rate pre and post exercise entered on each of the two levels of the factor shows that although there was a significant jump in pulse rate following the exercise across the whole sample ($F = 705.25$, $p < 0.00$, $df = 2$), there was no group x pulse rate change interaction ($F = 2.27$, $p = 0.11$, $df = 2$). In other words, all three groups were acutely stressed, as measured by their heart rate, to an equivalent degree.

Correlations with age and weight:

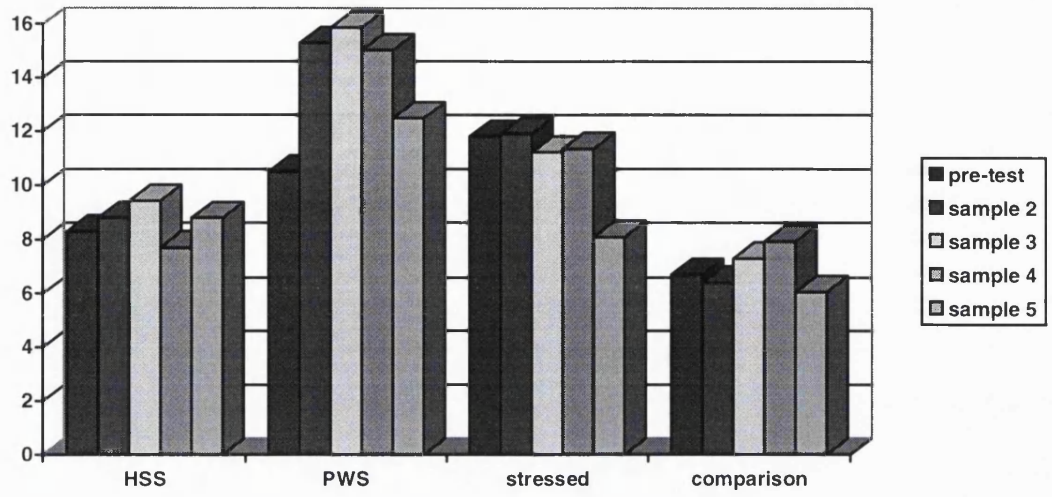
There was no significant relationship with baseline cortisol level and age ($r = 0.001$, $p = 0.99$). Nor was there any significant relationship in this sample between Body Mass Index and baseline cortisol ($r = -0.10$, $p = 0.44$) across the full sample or within the HSS ($r = -0.15$, $p = 0.51$), PWS ($r = -0.17$, $p = 0.44$) or stressed group (-0.07, $p = 0.77$).

A repeated measures ANOVA, described in table 4.3.4.2, shows that there was no significant differences in cortisol level across all 5 cortisol samples ($F = 1.33$, $p = 0.26$), nor was there any group x cortisol reaction interaction effect ($F = 0.96$, $p = 0.48$). This suggests that each group showed comparable HPA reaction and recovery following the acute stressor. (See figure 4.3.4.1.)

Table 4.3.4.2: Salivary cortisol: repeated measures ANOVA

	source of variance (df) F value and significance		
variable	*group (df=3)*	*cortisol reaction (df =4)*	*group x cortisol reaction (df = 12)*
cortisol	F = 0.69 p = 0.56	F = 1.33 p = 0.26	F = 0.96 p = 0.48

Figure 4.3.4.1: Cortisol reaction pattern following the acute stressor: group means



4.3.4.1 Summary

The hypothesis is not supported by the analyses. Groups showed comparable cortisol reactions following an acute stressor, irrespective of the children's stressed status.

4.4 Section B: Defining the HSS phenotype and comparing PWS and HSS

4.4.1 Cognitive ability

Hypothesis: *HSS and PWS are comparable in terms of cognitive ability, and distinct from the stressed group.*

Using four sub-scales from the WISC (Wechsler 1992) or WPPSI (Wechsler 1990), full scale, performance and verbal IQ scores were prorated. The group means are presented in table 4.4.1.1. In the HSS and stressed group particularly, there was a wide score range . HSS group IQ scores ranged from 50 to 118; and the score ranged between 46 and 121 for children in the stressed group. The range was 40 to 91 in the PWS group. 40 is the lowest IQ score in the WISC (41 in the WPPSI). It may be that if a cognitive test more appropriate for children with severe learning difficulties had been employed, the range of IQ scores may have been wider in the PWS group, and more similar to that observed in the other groups. 23 % of children with PWS (7 children) scored at the floor of the test.

Table 4.4.1.1: Full scale IQ, performance IQ and verbal IQ : group means

variable	*HSS (n=25) mean (sd)*	*PWS (n=30) mean (sd)*	*stressed (n=25) mean (sd)*
full IQ	77.66 (17.77)	53.97 (13.72)	84.17 (18.35)
performance IQ	83.40 (18.70)	56.00 (11.83)	88.29 (22.82)
verbal IQ	76.33 (18.21)	59.80 (16.63)	84.80 (18.10)

Table 4.4.1.2 describes the ANOVA analyses. There was a significant group effect ($F = 21.01$, $p < 0.000$) in full scale IQ. A post hoc Sheffe test shows that at an alpha of 0.05, both the stressed and the HSS group each have significantly higher full scale IQ scores when compared to the PWS group. The HSS group was not significantly different from the stressed group. There were no sex effects.

Table 4.4.1.2 : full scale IQ, performance IQ and verbal IQ: ANOVA analyses

variable	*source of variance, (df) F value and significance*		
	group (df = 2)	*sex* (df =1)	*group x sex* (df =2)
full scale IQ	F = 21.01 p < 0.00	F = 1.52 p = 0.22	F = 0.91 p = 0.41
performance IQ	F = 20.67 p < 0.00	F = 1.74 p = 0.19	F =1.77 p = 1.78
verbal IQ	F = 11.38 p < 0.00	F =1.10 p = 0.30	F = 1.04 p = 0.36

In verbal IQ and performance IQ, the pattern was similar: a significant main group effect, with both the HSS and stressed groups each having significantly higher performance IQ than the PWS group, at an alpha of 0.05.

***Correlations with age*:**

Correlations across the full sample did not show any significant relationship between age and cognitive ability. Full scale IQ (r = -0.01 p = 0.96), verbal IQ (r = -0.08, p = 0.46) and performance IQ (r = 0.06, p = 0.58) were all unrelated to age. In the HSS group correlation coefficients with age were as follows: full scale IQ: r = -0.09, p = 0.67, verbal IQ : r = -0.15, p = 0.48 and performance IQ: r = -0.07, p = 0.74. In the PWS group they were also insignificant (full scale IQ: r = -0.08, p = 0.68, verbal IQ: r = -0.07, p = 0.69 and performance IQ: r = -0.05, p = 0.78). In the stressed group, verbal IQ showed a significant negative correlation with age (-0.49, p = 0.01) but full scale IQ (r = -0.38, p = 0.07) and performance IQ (r = -0.11, p = 0.61) scores were unrelated to age.

Verbal and performance IQ discrepancies

The discrepancy between verbal and performance IQ was also examined across the groups. A difference of 11.5 points between the performance and verbal IQ scores reaches significance (0.05) (Wechsler 1992). 60% of the HSS group children, 50% of the stressed children and 27% of the PWS group children showed a significant difference between verbal and performance IQ. It is possible that by using four sub-scales, rather than the full test , that any discrepancy between verbal and performance abilities is exacerbated. Further Wechsler (1992) notes that such discrepancies are not

uncommon in the general population and are not necessarily *clinically* significant. A Pearson chi square showed that significantly fewer PWS children than stressed or HSS group children demonstrated a discrepancy (Pearson value 6.02, df = 2, p = 0.05). The independent cells within the 2 x 3 chi square were identified by calculating the contribution that each cell made to the total chi square value (appendix 10). The PWS group contributed the largest amount to the final chi square value.

Of those children who had a significant discrepancy, 78% of the children with HSS, 58% of the stressed group and 25% of the PWS group had a performance IQ significantly greater than their verbal ability. This pattern is often demonstrated in children who have emotional or behavioural difficulties (Wechsler, 1992). By the method described above, it was shown that significantly fewer PWS children showed this pattern as compared to the HSS or stressed children (Pearson value = 6.03, df = 2, p = 0.05).

4.4.1.1 Summary

These analyses raise two points. First there is no evidence to support the hypothesis that HSS and PWS are comparable in terms of cognitive ability. Further, significantly fewer children with PWS demonstrate a significant difference between verbal and performance ability suggesting there may be distinct cognitive profiles within each group. Second, there is no significant difference between the stressed and HSS groups' cognitive ability. The implications of this finding will be discussed in greater detail below.

Low IQ scores are associated with emotional and behavioural disturbance (eg Goodman, Simonoff, Stevenson, 1994), therefore it is important to control for this systematic difference between groups when examining psychosocial adjustment. IQ was entered as a covariate in all the following analyses, unless otherwise stated.

4.4.2. Anthropometric data

***Hypothesis**: The HSS and PWS groups are of significantly shorter stature than the stressed group.*

The anthropometric data group means are presented in table 4.4.2.1. ANOVA analyses were performed on these data and are described in table 4.4.2.2. A post hoc Sheffe test at an alpha level of 0.05, showed the nature of the significant group effect in standardised height. Each group was significantly different from one another. In other words, the HSS children were significantly shorter than both the PWS and stressed children and the PWS children were significantly smaller than the stressed children.

Table 4.4.2.1: Anthropometric data: group means

variable	*HSS (n=25) mean (sd)*	*PWS (n=27) mean (sd)*	*stressed (n= 22) mean (sd)*
*standardised height**	-2.63 (1.12)	-1.49 (1.49)	-0.12 (1.05)
*standardised body mass index**	-0.13 (1.15)	2.40 (1.97)	-0.23 (1.35)

** anthropometric data are standardised, allowing children of different ages to be compared directly*

Table 4.4.2.2: Anthropometric data: ANOVA analyses

	source of variance (df) F value & significance
variable	*group (df=2)*
standardised height	F = 23.59 p < 0.00
standardised body mass index	F = 23.33 p < 0.00

Body mass index:

Table 4.4.2.1 also illustrates that body mass index also showed a highly significant group effect. In this case, Sheffe post hoc tests indicated than the children with PWS had a significantly greater body mass index than either the stressed or the HSS groups. There was no significant difference between the stressed and HSS groups in terms of their body mass index.

Growth hormone therapy:

Six of the children in the PWS group took part in the study examining the effects of growth hormone on children with PWS, running at the Dunn Nutrition Unit (Cambridge). The children received GH injections for a trial period. There was no significant difference in terms of height ($t = 0.85$, $p = 0.40$), weight ($t = 1.42$, $p = 0.17$) or body mass index ($t = 1.05$, $p = 0.30$) between those children in the PWS group who had received growth hormone therapy and those who had not.

Body Mass Index correlations with hyperphagia and IQ.

General hyperphagia (parent report) and hyperphagia (school report) variables were summed (see 4.4.6) and then correlated with body mass index. There was a significant positive correlation across the whole sample ($r = 0.30$, $p = 0.01$), but within each group the relationship differed. There was no significant correlation in the HSS group ($r = 0.05$, $p = 0.80$) or in the stressed group ($r = 0.09$, $p = 0.68$) but the significant relationship remained for the children with PWS ($r = 0.38$, $p = 0.04$). There was no significant correlation between BMI and full scale IQ in the HSS group ($r = -0.18$, $p = 0.41$), the PWS group ($r = -0.12$, $p = 0.25$) or the stressed group ($r = -0.11$, $p = 0.62$).

4.4.2.1 Summary

The hypothesis is supported by the data. Children with HSS and PWS are significantly shorter than the stressed group. However, the analysis also shows that the HSS group are of shorter stature than the PWS group. Further, children with PWS have significantly greater body mass indices than either the HSS or the stressed groups, while the stressed and HSS groups have comparable BMIs.

4.4.3 Child Health History Factor Analysis

Variables relating to pregnancy and infant health from the HSSDI and the Child Health History Questionnaire were entered into a Principal Components Analysis (PCA), with varimax rotation. Table 4.4.3.1 illustrates the coefficients for each variable. In order to specify which of the individual variables which loaded onto each factor, a coefficient cut-off of 0.5 was used. Eigen values were set to be at least 1. Three factors were identified: weight gain problems/hypotonia with an Eigen value of 6.03, explaining 18.3% of the variance. Second 'milestones' which had an Eigen value of 2.92, explaining a further 8.9% of the variance. Third 'neonatal health' had an Eigen value of 2.8 and explained a further 8.4 % of the variance. Further factors were identified but were not employed in the analysis.

The PCA was used in order to identify which variables should be summed together, reducing the data. In other words, actual scores were used in the subsequent analyses rather than factor scores. On the basis of the PCA, variables were identified as correlated, and then summed. The summed data were labelled as described above. Where there were missing data, the full sample mean was substituted. 7 HSS, 2 PWS and 8 stressed cases had missing data on some variables either because questionnaires were not returned or foster/adoptive families did not have access to the relevant information.

Table 4.4.3.1: Factor analysis coefficient loadings for the child health factors

variable	*factor 1* ***weight gain probs/hypotonia***	*factor 2* ***milestones***	*factor 3* ***neonatal health***
weight gain problems	0.69	0.16	0.46
age at which child sat up	0.40	0.41	0.06
floppy head after 6 mths	0.84	0.36	0.12
unusual pregnancy	-0.14	-0.06	0.02
pregnancies surviving	-0.20	-0.06	-0.12
number of terminations	0.01	0.05	0.02
number of miscarriages	-0.08	-0.06	0.09
age: first smiled	-0.21	0.73	0.17
age: unsupported sitting	0.25	0.86	0.09
age: walked	0.41	0.64	-0.03
age: first words	0.12	0.83	-0.03
age: two word sentences	0.34	0.71	-0.01
gestation time	0.12	-0.07	-0.83
birthweight	-0.12	0.01	-0.85
hypotonia probs	0.80	0.38	0.05
forceps delivery	0.26	-0.10	0.03
caesarean delivery	0.25	0.04	0.17
other birth complications	0.22	0.19	0.10
special care baby unit	0.49	0.12	0.55
jaundice	0.13	-0.22	0.47
moth. discharged first	0.22	0.15	0.60
breast fed	0.11	-0.05	0.04
planned pregnancy	-0.17	0.06	0.16
termination considered	-0.06	-0.05	-0.10
adoption considered	0.03	-0.06	-0.18
kick chart used	0.04	-0.09	-0.17
smoking during	-0.69	0.05	0.16
drinking during	-0.09	-0.02	-0.03
suffered from nappy rash	-0.08	0.13	-0.03
gastric. probs	0.03	-0.18	-0.05
vomited frequently	-0.05	0.15	0.05
diarrhoea frequently	-0.09	0.03	0.01
fits or convulsions	0.31	-0.15	0.20

4.4.4 Child Health History

***Hypothesis**: HSS and PWS groups will be phenotypically similar in terms of infant health and distinct from the stressed group.*

Variables derived from factor analysis produced three summary variables: weight gain problems/hypotonia, milestones and neonatal health. In each case, a larger score indicates greater difficulties. For example, a relatively large milestones score indicated that the child's milestones were delayed. The group means are presented in table 4.4.4.1[1]. Group was entered as a factor for each of the ANOVA analyses. There was a significant group effect on all three variables (see table 4.4.4.2)

Table 4.4.4.1: Child Health History factors: group means[2]

variable	*HSS (n =25) mean (sd)*	*PWS (n=30) mean (sd)*	*stressed (n=25) mean (sd)*
weight gain probs/hypotonia	1.71 (1.80)	6.43 (1.16)	0.48 (1.02)
milestones	83.39 (34.59)	114.62 (47.55)	73.12 (22.60)
neonatal health	0.79 (0.74)	0.36 (0.81)	0.45 (0.55)

Table 4.4.4.2: Child Health History factors: ANOVA analyses

variable	*source of variance, (df) F value and significance*
weight gain probs/hypotonia	F = 149.66 p < 0.00
milestones	F = 9.43 p < 0.00
neonatal health	F = 11.44 p < 0.00

4.4.4.1 Weight gain problems/hypotonia

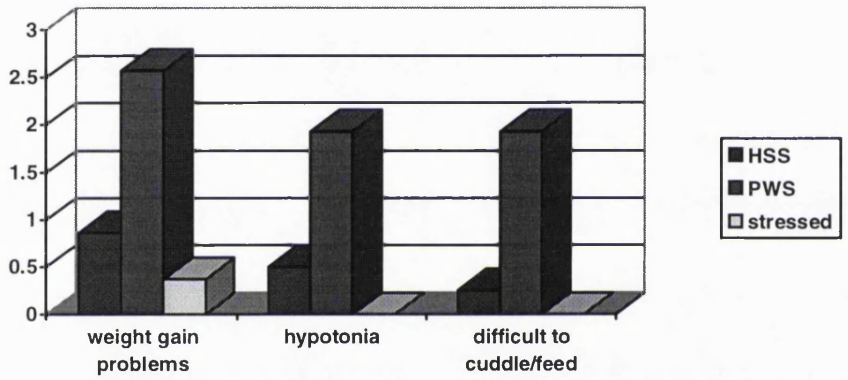
Post hoc analysis (Sheffe tests) showed that at an alpha of 0.05, each group was significantly different from one another on the weight gain problems/hypotonia variable. With the PWS group reporting more severe problems in this area (6.43 sd 1.16) than either the HSS group (1.74 sd 1.80) or the stressed group (0.48 sd 1.01). In addition, the HSS group showed significantly more problems than the stressed group.

[1] Data were unavailable for 7 HSS cases, 2 PWS and 8 stressed cases for some child health variables, due to adoptive/foster families lacking information or failure to return questionnaires

[2] where data were missing in the Child Health History, group mean replaced missing values

Clinical descriptions of HSS have included failure to thrive (eg Bowden and Hopwood 1982) but hypotonia is not documented as being associated with the condition. Therefore it was considered appropriate to examine this variable more closely, in order to examine the contribution of hypotonia and failure to thrive separately. Figure 4.4.2.1 demonstrates the distribution of scores within the weight gain problems/hypotonia summary variable. The range of scores on the hypotonia variable was 0 to 2, with '1' indicating that parents reported poor muscle tone but that medical professionals were not involved concerning the problem, while '2' indicated that medical professionals *were* involved.

Figure 4.4.2.1: Weight gain problems and hypotonia factor - the contribution from each variable: group means



93% (28 children) of the PWS group scored '2' compared to 16% (4 cases) of the HSS group. A similar picture emerges with the variable which describes whether the index child was difficult to cuddle because of floppy limbs, 93 % (28 cases) of the PWS sample responded indicating a score of '2' as compared to 13 % (3 cases) of the HSS sample. In both cases, 100% of the stressed group care-givers indicated there were no problems in these areas. Hypotonia can be a non-specific indicator of developmental delay (eg Georgieff, Bernbaum, Hoffman-Williamson and Daft, 1986). The children with HSS whose care-giver reported a score of 2, had a mean IQ of 64.5 (sd 13.08), ranging from 50 to 77.

Examination of the 'problems with weight gain' variable illustrates a more even distribution between the groups. 37% (n = 8) of caregivers reported that the HSS index child had failed to thrive, of these 14% were admitted to hospital to gain weight or to be tube fed. 87 % (26 cases) of the PWS children had failure to thrive, and of these 73% (22 cases) were admitted to hospital (or in some cases kept in hospital after birth) to

increase weight or to be tube fed. 8 % (2 cases) of the stressed children were failure to thrive and both children were admitted to hospital in order to gain weight. None of the stressed children were tube fed.

The data seem to indicate that hypotonia may differentiate the HSS and PWS groups to a greater degree than weight gain problems. A logistic regression was used to explore this issue, with the hypotonia variables presented dichotomously, as either requiring medical intervention or not. With both the hypotonia variables entered in the first step, and failure to thrive in the second, the model chi square improvement is not significant (model chi square value = 1.59, df = 2, p = 0.21). In order to confirm the contribution of the variables, this procedure was reversed, with failure to thrive entered in the first step, and both hypotonia variables in the second. The hypotonia variables improved the fit significantly (chi square model value = 29.86, df = 2, $p < 0.00$). This analysis confirms that the hypotonia variables, presented in the dichotomous form, distinguish the PWS from the HSS group to a greater degree than failure to thrive.

Failure to thrive as a dichotomous variable was explored in a chi square analysis. In other words, children were identified as failing to thrive or not. Some children may have had feeding difficulties according to caregivers, but may not have been identified as failure to thrive. A 2 x 3 chi square analysis, in order to examine the likelihood of failure to thrive was highly significant (Pearson chi square value 34.32, df = 2, $p < 0.00$). By examining the contribution that each group makes to the final chi square value (appendix 10), it is clear that the stressed group are significantly less likely to fail to thrive than the PWS or HSS group. However, if the chi square value contribution that the stressed group make is subtracted from the final chi square value, the chi square (value 19.64 df =1) remains significant at $p < 0.05$. This indicates that the children with PWS are significantly more likely to fail to thrive in infancy than children with HSS.

4.4.4.2 Milestones and neonatal health

In the 'milestones' summary variable, the significant comparisons were between the PWS group and both the stressed and HSS group, with the PWS group being significantly delayed in terms of reaching milestones. A similar comparison was evident in neonatal health using a Sheffe post hoc test. PWS children had significantly more neonatal health problems than either the HSS or the stressed group.

4.4.4.3 Birthweight

There were no significant group differences in the birthweight of the index children (F = 1.28, p = 0.29). This non-significant effect was maintained with the ordinal position of the index child as a covariate. There was a trend for the PWS children to have the lowest birthweight (92.87 ounces, sd 23.23) followed by the HSS group (99.18 ounces, sd 31.31) and finally the children in the stressed group (105.86 ounces sd 25.91). There was one outlier in the HSS and one in the stressed group, in terms of low birthweight. Both these children were excluded from the sample, to make 'new' group means of 104.19 ounces (sd 24.30), and 105.23 ounces (sd 26.62) respectively for the HSS and stressed group. The non-significant group differences remained, even excluding the two outliers (F = 1.72. p = 0.18).

61% of HSS group biological mothers, 76 % of stressed group and 21% of PWS group mothers smoked during their pregnancy. Examination of the contribution that each cell makes to the final chi square value (appendix 10) indicates that the PWS group were significantly less likely to smoke than either of the other two groups. (Pearson chi square value = 14.69, df = 2, p< 0.00). There were no significant differences across the groups in the frequency of mothers drinking during the pregnancy. 17%, 32% and 35% of HSS, PWS and stressed group mothers respectively, reported that they drank alcohol during their pregnancy. Smoking may decrease birthweight by around 5%. Birthweight is also reduced in cases in which mother's drink alcohol during pregnancy, but the effect is not significant once smoking is controlled. Finally maternal height can also influence birthweight significantly (Brooke, Anderson, Bland, Peacock, Stewart, 1989). To explore these issues further using a linear regression and the full group data, maternal height was regressed out (F = 0.20, p = 0.66) and then the presence or absence of drinking or smoking during pregnancy was entered as a dummy variable (F = 0.124, p = 0.94). Neither maternal height nor drinking and smoking were found to have contributed significantly to the variance in birth weight.

4.4.4.4 Gestation time.

Nor were there any group differences in terms of the gestation period of the index children (F = 0.67, p = 0.52). Group means for the HSS, PWS and stressed groups were 36.50 weeks gestation (sd 3.42), 37.46 (sd 3.54) and 37.94 (sd 3.90) respectively.

4.4.4.5 Pregnancies surviving birth

The number of pregnancies that survived birth was also recorded and analysed as a percentage of the total number of times that the index child's biological mother had been pregnant. All data were, as before, from each index child's biological mother. 84.53 % (sd 24.77) of pregnancies survived birth in the HSS group, as compared to 81.78% (sd 25.96) in the PWS group and 85.87% (sd 24.34) in the stressed group. There were no significant group differences ($F = 0.15$, $p = 0.86$).

4.4.4.6 Summary

These analyses do not, on the whole support the hypothesis that children in the HSS and PWS groups are phenotypically similar in terms of child health. On many variables the HSS group were distinct from the PWS group and not significantly different from the stressed group. Although the PWS group are more likely to fail to thrive, show hypotonia and have weight gain problems, according to care-giver report, than the HSS group, the HSS group were more likely to show such problems than the stressed group.

4.4.5 Hyperphagia and appetite disturbance (parent and teacher report) factor analysis

Variables relating to appetite from the HSSDI and the school report (completed by teachers) were entered into a Principal Components Analysis (PCA), with varimax rotation. Table 4.4.5.1 illustrates the coefficients for each variable. In order to specify which individual variables loaded onto each factor, a coefficient cut-off of 0.4 was used. Eigen values were set to be at least 1. Four factors were identified: 'general hyperphagia' with an Eigen value of 4.32, explaining 33.2% of the variance. Second 'school hyperphagia' which had an Eigen value of 2.04, explaining a further 15.7% of the variance. Third 'pica/polydipsia' had an Eigen value of 1.26 and explained a further 9.7 % of the variance. Fourth 'other hyperphagia' which had an Eigen value of 1.13 and accounted for a final 8.8% of the variance.

The PCA was used in order to identify which variables should be summed together, and so reducing the data. In other words, actual scores were used in the subsequent analyses rather than factor scores. On the basis of the PCA, variables were identified as being correlated, and then summed. The summed data were labelled as described above. Data were unavailable from one PWS and three stressed children's school. One further family in the PWS group requested that their son's school should not be contacted. Full sample means were substituted for these missing values. There were no missing data for the HSSDI variables.

Table 4.4.5.1: Factor analysis coefficient loadings on hyperphagia factors

variable	*factor 1* ***general hyperphagia***	*factor 2* ***school hyperphagia***	*factor 3* ***pica/polydipsia***	*factor 4* ***other hyperphagia***
stealing food: kitchen cupboards	0.91	0.13	0.04	-0.06
stealing food: fridge	0.92	0.11	0.09	-0.09
stealing food: plates at mealtimes	0.63	0.14	0.34	0.30
hoarding food	0.55	-0.04	-0.15	0.31
stealing food: school	0.39	0.55	-0.12	0.53
overeating requiring restraint	0.69	0.13	0.003	0.20
gorging and vomiting	0.28	0.31	0.11	0.50
polydipsia	0.11	-0.03	0.78	0.24
pica	0.55	-0.04	0.44	0.06
chewing non-food items	-0.05	-0.11	0.21	0.82
pica: school report	-0.003	0.50	0.72	-0.01
eating non food items: school report	-0.03	0.70	0.54	-0.06
stealing food: school report	0.14	0.88	0.02	0.04

4.4.6 Hyperphagia and appetite disturbance (parent and teacher report)

4.4.6.1 The degree of appetite disturbance

Hypothesis: *PWS and HSS groups will be phenotypically similar in terms of the degree and quality of hyperphagia and appetite disturbance.*

Hypothesis*: Hyperphagia is not a normative response to stress.*

The variables derived from the PCA described in 4.4.5 were used in the following analyses.

IQ as a covariate:

In order to explore the relationship between hyperphagia and IQ, Pearson bivariate correlations were performed within each group. IQ did not correlate significantly with any of the four aspects of hyperphagia the three groups. Correlation coefficents for hyperphagia at school, general hyperphagia, pica/polydipsia and 'other hyperphagia' were all non-significant (r = -0.08, p = 0.71, r = 0.09, p = 0.67, r = -0.25, p = 0.25 and r = -0.03, p = 0.90 respectively) in the HSS group. In the PWS group the correlation coefficents were as follows: r = -0.26,(p = 0.16), r = -0.15, (p = 0.41), r = -0.08, (p = 0.65) and r = -0.08, p = (0.71). The stressed group showed a similar pattern (r = -0.23, p = 0.27, p = 0.06, p = 0.80, r = 0.10, p = 0.65, r = 0.30, p = 0.15). However as there was a significant difference in the groups' cognitive ability (see 4.4.1.1), IQ was entered as a covariate in all four analyses, and therefore, held constant across the groups. Post hoc tests were performed on group means with IQ regressed out.

The group means for each of the summed variables, derived from factor analyses, describing parental and teacher report of various aspects of hyperphagia are described in table 4.4.6.1. Each variable was entered into an ANOVA analysis with group and sex entered as factors. Table 4.4.6.2 describes these analyses. Significant group effects were found in all four variables: school hyperphagia, general hyperphagia and pica/polydipsia and 'other hyperphagia'. Sheffe post hoc tests were applied to identify the specific significant interaction. In the general hyperphagia analysis, at a significance level of 0.05, both the HSS group and the PWS group had a significantly greater number of hyperphagic features when compared to the stressed children. In 'other hyperphagia' only the HSS group was significantly more likely to show appetite disturbance than the stressed group. At school, according to both parents and teachers,

the HSS group was significantly more likely to demonstrate hyperphagia than the stressed group, but the stressed group was not significantly different from the PWS group. In terms of pica/polydipsia, as before, the HSS group showed significantly more difficulties in this area than the stressed group. None of the sex effects proved to be significant.

Table 4.4.6.1: Hyperphagia factors group means

variable	*HSS (n=25) mean (sd)*	*PWS (n=30) mean (sd)*	*stressed (n=25) mean (sd)*
school hyperphagia	5.52 (2.57)	5.07 (2.65)	2.80 (1.35)
general hyperphagia	11.00 (5.00)	9.88 (3.85)	2.79 (3.24)
pica and polydipsia	5.61 (2.78)	4.82 (2.19)	3.07 (1.47)
other hyperphagia	3.71 (2.79)	2.83 (2.52)	1.04 (0.93)

Table 4.4.6.2: Hyperphagia factors: ANOVA analyses

variable	*Source of variance (df) F value and significance*		
	group (df =2)	*sex (df=1)*	*group x sex (df=2)*
school hyperphagia	F= 5.61 p= 0.01	F= 0.31 p = 0.58	F = 0.06 p = 0.95
general hyperphagia	F = 23.17 p < 0.00	F = 0.09 p = 0.77	F = 0.77 p = 0.47
pica and polydipsia	F = 8.75 p < 0.00	F = 0.03 p = 0.87	F = 2.21 p = 0.12
other hyperphagia	F = 6.40 p < 0.00	F = 0.06 p = 0.81	F = 0.35 p = 0.70

Correlation with age:

Each of the four variables, with IQ regressed out, were correlated with age across the full sample. Correlations with general hyperphagia (r = -0.02, p = 0.85) hyperphagia at school (r = -0.178 p = 0.11) pica/polydipsia (r = -0.20 p = 0.07) and 'other hyperphagia' (r = -0.09,p= 0.42) all proved to be non-significant. Correlations within each group showed the same pattern, with one exception. In the HSS group, age correlations with general hyperphagia (r = -0.18,p = 0.40) hyperphagia at school (r = -0.14, p = 0.49) and 'other hyperphagia' (r = 0.02,p= 0.94) were not significant. However, there was a significant negative age correlation with pica/polydipsia (r = -0.55 p = 0.01), with younger children reported as having more difficulties in this area. None of the correlations with

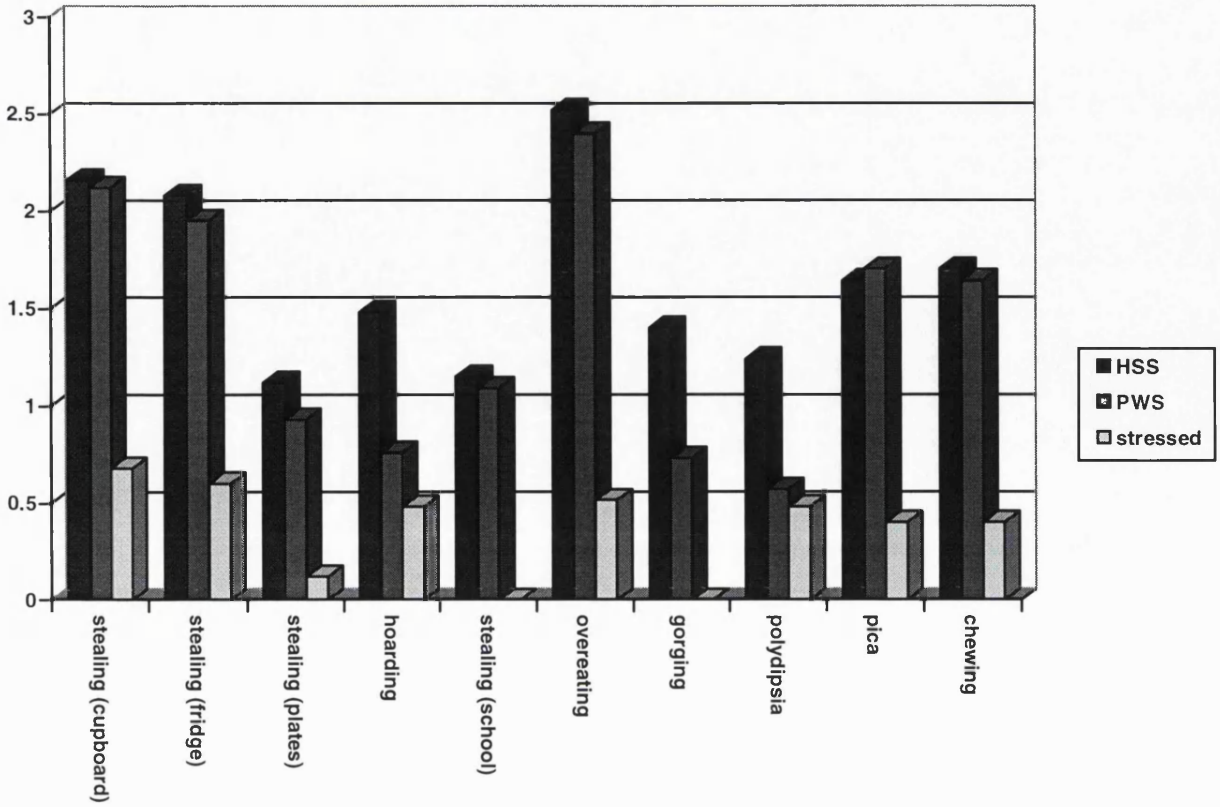
age proved significant in the PWS group (general hyperphagia (r = -0.02,p = 0.92) hyperphagia at school (r = -0.11, p = 0.58) pica/polydipsia (r = -0.25 p = 0.19) and 'other hyperphagia' (r = -0.03, p= 0.87)). In the stressed group there was a similar picture with all relationships between age and symptoms proving insignificant (general hyperphagia, r = 0.28, p = 0.19, hyperphagia at school, r = -0.06, p = 0.78 pica/polydipsia, r = -0.15 p = 0.50 and 'other hyperphagia' r = -0.01, p= 0.95).

The analyses described supports both hypotheses. Stressed children were significantly less likely to show appetite disturbance in comparison to the HSS group, according to parental and teacher report. This indicates that hyperphagia may be a specific reaction to stress and not a normative response, even in children with a relatively low IQ. There may be a case for suggesting that children with HSS have more disturbed eating patterns in some domains than children with PWS according to care-givers, as in 3 of four comparisons, the HSS children and not the children with PWS were reported to have significantly greater appetite disturbance than the stressed children.

4.4.6.2 The quality of appetite disturbance

Figure 4.4.6.1: item profile of appetite disturbance by group

In order to examine more closely the qualitative similarities between the PWS and HSS



group appetite profiles, an item by item analysis was undertaken. Figure 4.4.6.1 shows graphically that there is a similar profile across the PWS and HSS groups in terms of their appetite disturbance. Table 4.4.6.3 describes the group means for each item, however the emphasis in this analysis concerns the *quality* of appetite disturbance rather than the severity of that disturbance. A series of ANOVA tests[3] (with IQ as a covariate) were done. Sheffe post hoc tests at a significance level of 0.05 show that in stealing food from cupboards ($F = 12.00$, $p < 0.00$), the fridge ($F = 10.31$, $p = < 0.00$), plates ($F = 6.94$, $p = < 0.001$) , at school ($F = 5.97$, $p < 0.00$) , in overeating, requiring restraint ($F = 18.53$, $p < 0.00$) and in pica ($F = 5.20$, $p = 0.01$), the PWS and HSS groups were not significantly different from one another, but both groups showed significantly more disturbance in these areas than the stressed group. The HSS group were significantly more likely to hoard food than the stressed group ($F = 4.36$, $p = 0.02$). The HSS group were more likely to gorge *and vomit* than both the stressed and the PWS group ($F = 8.16$, $p < 0.00$). The children with HSS were significantly more likely to be polydipsic than both the stressed or the children with PWS ($F = 5.05$, $p = 0.01$). There were no significant group differences on the chewing variable ($F = 0.25$, $p = 0.78$).

Table 4.4.6.3: Appetite disturbance items: group means

variable	*HSS (n=25) mean (sd)*	*PWS (n=30) mean (sd)*	*stressed (n=25) mean (sd)*
stealing food from cupboards	2.16 (1.07)	2.12 (0.90)	0.68 (0.90)
stealing food from the fridge	2.08 (1.15)	1.95 (1.04)	0.60 (0.91)
stealing food from plates	1.12 (1.24)	0.93 (0.87)	0.12 (0.44)
hoarding	1.48 (1.42)	0.77 (1.19)	0.48 (1.04)
stealing food from school	1.15 (1.31)	1.09 (1.19)	0.00 (0.00)
overeating	2.52 (0.96)	2.40 (1.22)	0.51 (0.91)
gorging and vomiting	1.40 (1.50)	0.73 (1.20)	0.00 (0.00)
polydipsia	1.24 (1.23)	0.57 (0.86)	0.48 (0.87)
pica	1.64 (1.35)	1.70 (1.24)	0.40 (0.96)
chewing non-food	1.16 (1.14)	1.00 (1.08)	1.04 (0.93)

[3] Parametric ANOVAs were used as the HSSDI variables are on an interval scale, with equal distance between points.

4.4.6.3 Summary

In sum, these analyses provides further evidence, that in terms of appetite disturbance the HSS and PWS group show remarkably similar behavioural profiles, which are distinct from the stressed group. On some variables children with HSS show a greater degree of appetite disturbance than the PWS group.

4.4.7 Self-reported and observed psychosocial profile (CAS Hodges,1978)

***Hypotheses**: HSS and PWS group children will have a distinctive pattern of self-reported and observed psychosocial adjustment in comparison to the stressed group.*

Because there were group specific differences in cognitive ability (see 4.4.1), in each ANOVA analysis, IQ was covaried. Sex effects were also explored, in addition to group effects. Investigation of sex differences in child reported psychopathology was considered important in view of the literature documenting gender issues. However, by splitting the groups in order to search for interaction effects, the numbers in each group are reduced dramatically, and therefore caution is needed in interpreting the results.

A number of children were not administered the CAS as they were aged under six years old, the minimum age at which the CAS may be used (Hodges, personal communication). One child with HSS used English as a second language and therefore was not able to complete the CAS. 12 children in the PWS group functioned below the level required to complete the interview reliably. Interestingly, this group did not have a significantly lower IQ than those who were able to complete the interview (50.25 sd 12.57 and 56.08 sd 15.22 respectively, $t = 1.02$, $p = 0.32$). This may provide further evidence that IQ scores do not accurately reflect many important aspects of functioning (American Association on Mental Retardation, 1992).

In each analysis, the greater the CAS score the greater the degree of reported or observed psychosocial adjustment difficulty.

***Multiple contrasts**:*

Because so many contrasts (26 in total) were performed on the CAS data, dividing the same items in different ways as described below, it was considered appropriate to apply the Bonferonni correction to the alpha value of 0.05. This correction takes into account the increased likelihood of a type I error following multiple testing. The alpha of 0.05 was divided by the number of contrasts (in this case 26), making a corrected alpha of 0.002 (Bland & Altman, 1995). Any comparison reaching significance at the corrected level is regarded as, being in fact significant at the uncorrected level ie 0.05. In order words, there remains a one in twenty probability that the finding is significant by chance.

4.4.7.1 Total CAS items endorsed

The items from the CAS (Hodges 1978) were grouped and analysed in a number of ways. First the total number of CAS items endorsed, summing both child report and observational items (scored by the interviewer on the basis of behaviour during the interview) was tested. In addition, the total observed items and total child report items were analysed separately. Group means for each of the score are reported in table 4.4.7.1.

Table 4.4.7 1: CAS total score, child report items score and observational items score: group means

variable	*HSS (n = 20) mean (sd)*	*PWS (n = 13) mean (sd)*	*stressed (n=20) mean (sd)*
CAS total score	38.85 (11.32)	31.69 (12.46)	34.66 (11.88)
CAS child report items total score	32.50 (11.51)	25.77 (12.32)	31.38 (10.95)
CAS observational items total score	6.35 (4.42)	5.92 (2.63)	3.29 (3.44)

There were no group, sex or interaction effects on any of the CAS total items summaries, using the corrected alpha level. These ANOVA analyses are described in table 4.4.7.2.

Table 4.4.7.2: CAS total score, child report items score and observational items score: ANOVA analyses.

	source of variance (df), F value and significance		
variables	group (df = 2)	sex (df = 1)	group x sex (df = 2)
total score	F = 1.41 p = 0.25	F = 6.68 p = 0.01	F = 0.24 p = 0.79
child report score	F = 1.11 p = 0.34	F = 5.51 p = 0.02	F = 0.45 p = 0.64
observational items	F = 2.93 p = 0.06	F = 0.81 p= 0.37	F = 0.51 p = 0.60

4.4.7.3 CAS content areas

The CAS was also analysed in terms of question content area. Content areas covered in the child report section were: school, friends, family, fears, worries, self-image, mood physical complaints and acting out. Hodges et al (1978) analysed data using this particular categorisation. The observed items content scales included: activity level, communication, emotional response, behavioural response and inter-personal response. Table 4.4.7.3 illustrates the group means for each of these areas.

Table 4.4.7.3: CAS content areas: group means

variable	*HSS (n = 20) mean (sd)*	*PWS (n = 13) mean (sd)*	*stressed (n =24) mean (sd)*
school	3.35 (2.43)	2.85 (2.48)	3.21 (2.43)
friends	2.40 (1.57)	2.53 (2.14)	2.50 (1.47)
family	5.40 (2.48)	5.13 (2.23)	5.41 (3.52)
fears	1.35 (1.31)	0.62 (0.77)	0.75 (0.85)
worries	5.15 (2.06)	3.23 (1.96)	3.92 (1.95)
self image	2.95 (1.61)	1.92 (1.38)	3.17 (2.01)
mood	4.20 (3.19)	3.31 (3.06)	4.67 (2.78)
physical symptoms	2.85 (2.70)	3.15 (2.23)	2.54 (2.21)
acting out	4.85 (3.44)	3.00 (2.42)	5.21 (2.90)
*activity level**	1.85 (2.54)	1.23 (0.60)	0.79 (1.47)
*communication**	1.60 (1.31)	2.69 (1.70)	1.08 (1.38)
*emotional response**	0.65 (0.93)	0.15 (0.38)	0.29 (0.69)
*behavioural response**	0.80 (0.77)	0.54 (0.66)	0.38 (0.49)
*interpersonal response**	0.85 (2.00)	0.31 (0.48)	0.29 (0.55)

* *observed items*

Table 4.4.7.4 documents the series of ANOVA analyses performed on the content areas. With the corrected alpha at 0.002, there were no significant group, sex or interaction effects.

Table 4.4.7.4: CAS content areas: ANOVA analyses

	source of variance (df), F value and significance		
variables	group (df = 2)	sex (df = 1)	group x sex (df = 2)
school	F = 0.68 p = 0.51	F = 1.16 p = 0.29	F =3.92 p = 0.03
friends	F = 0.31 p = 0.74	F = 0.02 p = 0.88	F = 0.66 p = 0.52
family	F = 0.19 p = 0.83	F = 2.81 p = 0.10	F = 0.01 p = 0.99
fears	F = 2.04 p = 0.14	F =1.02 p = 0.32	F = 0.12 p = 0.89
worries	F = 2.22 p = 0.12	F = 1.33 p = 0.25	F = 0.97 p = 0.38
self image	F = 3.75 p = 0.03	F = 2.91 p = 0.09	F = 1.23 p = 0.30
mood	F = 1.75 p = 0.18	F = 1.60 p = 0.21	F = 3.56 p = 0.04
physical symptoms	F = 0.62 p = 0.54	F = 1.50 p = 0.23	F = 0.78 p = 0.46
acting out	F = 2.36 p = 0.10	F = 4.69 p = 0.04	F = 0.17 p = 0.85
*activity level**	F = 3.35 p = 0.04	F = 0.73 p = 0.40	F = 2.33 p = 0.11
*communication**	F = 1.10 p = 0.34	F = 1.29 p = 0.26	F = 0.13 p = 0.88
*emotional response**	F = 2.96 p = 0.06	F = 3.98 p = 0.05	F = 0.16 p = 0.85
*behavioural response**	F = 2.76 p = 0.07	F = 4.58 p = 0.04	F = 1.31 p = 0.28
*interpersonal response**	F = 0.56 p = 0.58	F = 0.15 p = 0.70	F = 0.77 p = 0.47

** observed items*

4.4.7.3 CAS symptom complexes

Individual items from both the child reported and observational sections are drawn together to relate to syndromes described in DSM III. These symptom complexes do not constitute a diagnosis of any one syndrome. The items relating to each syndrome were summed to give a score on an interval scale (see table 4.4.7.5). Some items appear in more than one complex. Symptom complexes covered were: attention deficit with and without hyperactivity, conduct disorder (undersocialised, socialised, aggressive and non-aggressive), separation anxiety, overanxious disorder and 'other' disorder.

Table 4.4.7.5: CAS symptom complexes: group means

variable	*HSS (n = 20) mean (sd)*	*PWS (n = 13) mean (sd)*	*stressed (n = 24) mean (sd)*
attention deficit with hyperactivity	2.55 (2.35)	1.54 (0.97)	1.75 (1.70)
attention deficit, no hyperactivity	2.00 (1.59)	1.38 (1.04)	1.14 (1.38)
conduct disorder: undersocialised, aggressive	2.20 (1.82)	2.00 (1.91)	2.33 (1.68)
conduct disorder: undersocialised, non-aggressive	1.95 (1.82)	1.15 (0.99)	2.00 (1.53)
conduct disorder: socialised, aggressive	1.50 (1.57)	1.00 (1.29)	1.71 (1.54)
conduct disorder: socialised, non-aggressive	1.20 (1.47)	0.15 (0.38)	1.46 (1.56)
separation anxiety	3.55 (2.42)	1.77 (1.92)	2.21 (1.41)
overanxious disorder	3.55 (1.67)	2.31 (2.02)	2.79 (1.93)
other disorder	1.95 (1.31)	1.00 (1.29)	1.54 (1.32)

Table 4.4.7.6 : CAS symptom complexes: ANOVA analyses

	source of variance (df), F value and significance		
variables	group (df = 2)	sex (df = 1)	group x sex (df = 2)
attention deficit with hyperactivity	F = 2.96 p = 0.06	F = 1.01 p = 0.32	F = 2.51 p = 0.09
attention deficit, no hyperactivity	F = 2.43 p = 0.10	F = 0.34 p = 0.56	F = 2.88 P = 0.06
conduct disorder: undersocialised, aggressive	F = 2.43 p = 0.10	F = 3.08 p = 0.08	F = 0.40 p = 0.67
conduct disorder: undersocialised, non-aggressive	F = 1.25 p = 0.30	F = 1.35 p = 0.25	F = 0.44 p = 0.65
conduct disorder: socialised, aggressive	F = 1.48 p = 0.24	F = 6.98 p = 0.01	F = 0.38 p = 0.68
conduct disorder: socialised, non-aggressive	F = 3.74 p = 0.03	F = 1.57 p = 0.22	F = 0.24 p = 0.79
separation anxiety	F = 3.36 p = 0.04	F = 3.59 p = 0.06	F = 2.23 p = 0.12
overanxious disorder	F = 1.45 p = 0.24	F = 6.77 p = 0.01	F = 0.53 p = 0.59
other disorder	F = 1.86 p = 0.17	F = 2.22 p = 0.14	F = 0.71 p = 0.50

Table 4.4.7.6 describes the ANOVA analyses, with group and sex as factors. Using the corrected alpha, none of the symptom complex scores reached significance on either the main effects or interaction effects.

Correlations with age:

The literature describes age related trends in psychopathology (eg Rutter et al 1976), and therefore Pearson two-tailed correlations between each sub-scale and age across the full sample and within each group were performed. Table 4.4.7.7 describes the correlations. In order to avoid type I errors as described above, the same Bonferroni correction was applied to the alpha level. Across the full sample, there was a significant positive correlation ($r = 0.43$, $p < 0.00$) between total child reported adjustment difficulties and age. The positive significant relationship held for mood ($r = 0.56$, $p <$

0.00), acting out ($p < 0.00$) , conduct disorder, undersocialised non-aggressive ($r = 0.46$, $p < 0.00$), conduct disorder, undersocialised, aggressive ($r = 0.54$, $p < 0.00$) conduct disorder socialised non-aggressive ($r = 0.60$, $p < 0.00$) and 'other disorder' ($r = 0.44$, $p < 0.00$), suggesting that symptoms in these areas were significantly more frequent in older children . There were a number of areas in which the effect was in the opposite direction. Activity level ($r = -0.50$, $p < 0.00$) and attention deficit with hyperactivity ($r = -0.43$, $p < 0.00$) both showed an inverse relationship with age, with older children showing fewer symptoms.

Correlations between age and sub-scale scores showed a different pattern within each of the three groups. Children with HSS were described as having a positive significant correlations between age and the acting out ($r = 0.69$, $p < 0.00$) conduct disorder, undersocialised aggressive ($r = 0.66$, $p < 0.00$) and conduct disorder, socialised non-aggressive ($r = 0.67$, $p < 0.00$) sub-scale scores. Using the corrected alpha level, there were no significant correlations between sub-scale scores and age in the PWS group. The stressed group, like the HSS group, also showed positive significant correlations with age in the acting out sub-scale ($r = 0.66$, $p < 0.00$), conduct disorder, undersocialised aggressive ($r = 0.61$, $p < 0.00$) conduct disorder, and socialised non-aggressive ($r = 0.79$, $p < 0.00$). There were a number of other significant positive relationships between sub-scale scores and age in the stressed group. Conduct disorder, undersocialised non-aggressive ($r = 0.54$, $p < 0.00$) and 'other' disorder ($r = 0.57$, $p < 0.00$) sub-scale scores both increased significantly with the age of the child assessed.

4.4.7.4 Summary

These analyses do not support the hypothesis that children with HSS and PWS have a distinctive psychopathology in comparison to the stressed group. There is stronger evidence to suggest age related changes in child reported and observed psychosocial adjustment. This was particularly true for the stressed group and to a lesser degree, the children with HSS . In activity orientated sub-scales younger children demonstrated most difficulty. For the remainder of significant correlations, symptoms increased with age, suggesting puberty may be a significant factor in the onset of some psychosocial symptoms.

Table 4.4.7.7: Correlations with age: full sample and within groups

sub-scale	*full sample*	*HSS*	*PWS*	*stressed*
CAS total score	r = 0.32 p = 0.02	r = 0.23 p = 0.33	r = 0.51 p = 0.08	r = 0.38 p = 0.06
CAS child report items total score	r = 0.43 p < 0.00	r = 0.38 p = 0.09	r = 0.52 p = 0.06	r = 0.49 p = 0.02
CAS observational items total score	r = -0.30 p = 0.02	r = -0.42 p = 0.07	r = -0.05 p = 0.87	r = -0.25 p = 0.24
school	r = 0.18 p = 0.18	r = 0.08 p = 0.72	r = 0.45 p = 0.12	r = 0.14 p = 0.51
friends	r = -0.01 p = 0.93	r = 0.08 p = 0.73	r = 0.43 p = 0.14	r = -0.45 p = 0.03
family	r = 0.14 p = 0.29	r = -0.06 p = 0.81	r < 0.00 p = 0.99	r = 0.33 p = 0.12
fears	r = 0.01 p = 0.92	r < 0.00 p = 0.98	r = -0.09 p = 0.75	r = 0.18 p = 0.41
worries	r = 0.07 p = 0.58	r = -0.03 p = 0.91	r = 0.28 p = 0.36	r = 0.17 p = 0.42
self image	r = 0.30 p = 0.03	r = 0.40 p = 0.08	r = 0.61 p = 0.03	r = 0.15 p = 0.48
mood	r = 0.43 p < 0.00	r = 0.32 p = 0.16	r = 0.63 p = 0.02	r = 0.45 p = 0.03
physical symptoms	r = 0.19 p = 0.16	r = 0.09 p = 0.71	r = 0.31 p = 0.30	r = 0.26 p = 0.22
acting out	r = 0.56 p < 0.00	r = 0.69 p < 0.00	r = 0.19 p = 0.52	r = 0.66 p < 0.00
activity level	r = -0.50 p < 0.00	r = -0.56 p = 0.01	r = -0.57 p = 0.04	r = -0.48 p = 0.02
communication	r = -0.07 p = 0.63	r = 0.05 p = 0.84	r = -0.10 p = 0.74	r = -0.14 p = 0.52
emotional response	r = 0.08 p = 0.54	r = 0.02 p = 0.95	r = 0.48 p = 0.10	r = 0.14 p = 0.52
behavioural response	r = -0.04 p = 0.78	r = -0.06 p = 0.78	p = 0.11 p = 0.73	r < -0.00 p = 0.96
interpersonal response	r = -0.12 p = 0.38	r = -0.16 p = 0.51	p = 0.17 p = 0.57	r = -0.11 p = 0.63
attention deficit with hyperactivity	r = -0.43 p < 0.00	r = -0.53 p = 0.02	r = -0.51 p = 0.08	r = -0.28 p = 0.18
attention deficit, no hyperactivity	r = -0.30 p = 0.03	r = -0.52 p = 0.02	r = -0.30 p = 0.34	r = -0.04 p = 0.86
conduct disorder: undersocialised, aggressive	r = 0.31 p = 0.02	r = 0.39 p = 0.09	r = 0.40 p = 0.19	r = 0.19 p = 0.38
conduct disorder: undersocialised, non-aggressive	r = 0.46 p < 0.00	r = 0.47 p = 0.04	r = 0.40 p = 0.17	r = 0.54 p < 0.00
conduct disorder: socialised, aggressive	r = 0.54 p < 0.00	r = 0.66 p < 0.00	r = 0.18 p = 0.55	r = 0.61 p < 0.00
conduct disorder: socialised, non-aggressive	r = 0.60 p < 0.00	r = 0.67 p < 0.00	r = -0.09 p = 0.76	r = 0.79 p < 0.00
separation anxiety	r = 0.17 p = 0.20	r = 0.24 p = 0.30	r = -0.07 p = 0.81	r = 0.42 p = 0.04
overanxious disorder	r = 0.35 p = 0.01	r = 0.28 p = 0.23	r = 0.27 p = 0.37	r = 0.54 p = 0.01
other disorder	r = 0.44 p < 0.00	r = 0.53 p = 0.02	r = 0.22 p = 0.47	r = 0.57 p < 0.00

4.4.8 Behaviour disturbance (parent and teacher report) factor analysis

Variables were selected relating to behavioural disturbance from the HSSDI and the teacher completed school report and Difficult Behaviour Questionnaire. These were entered into a Principle Components Analysis (PCA), with varimax rotation. Six factors were identified. The loadings on each variable for the factors are described in table 4.4.8.1. A coefficient value cut-off of 0.4 was used. Eigen values were set to be at least 1. Factor 1 was identified as 'soiling/wetting at school', it had an Eigen value of 4.47 and explained 22.4% of the variance. The second factor was labelled 'externalising at school', this factor explained a further 14.4% of the variance and had an Eigen value of 2.88. General externalising (ie at home and school), the third factor explained a further 10.1% of the variance and had an Eigen value of 2.03. Factor 4 was labelled 'attention and overactivity problems at school' (Eigen value = 1.70, 8.5% variance explained). General attention and overactivity problems (at home and school) was the fifth factor and had an Eigen value of 1.31, explaining 6.5 % of the variance. The final factor, soiling/wetting at home, explained a final 6.0% of the variance and had an Eigen value of 1.19.

The PCA was employed in order to identify which variables were related to one another. These variable values, rather than factor scores, were then summed and labelled as described above. Missing values were replaced by the full sample mean. One school from the PWS group and 3 from the stressed group failed to return their questionnaires. One further family in the PWS group requested that their son's school should not be contacted. All the schools in the HSS group returned questionnaires, and there were full data in the HSSDI for all cases.

Table 4.4.8.1: Factor analysis coefficient loadings on the behavioural disturbance factors

variable	*factor 1* ***soils/wets at school***	*factor 2* ***externalising at school***	*factor 3* ***general externalising***	*factor 4* ***attention/ overactivity problems in school***	*factor 5* ***general attention/ overactivty problems***	*factor 6* ***soils/wets at home***
stealing at home	-0.32	0.22	0.69	0.15	-0.05	0.09
destruction at home	0.11	0.09	0.74	0.04	0.18	0.07
temper tantrums at home	0.10	-0.03	0.73	-0.09	0.22	0.16
enuresis at home	-0.03	0.03	-0.01	0.09	0.13	0.81
encopresis at home	0.30	0.01	0.12	0.04	-0.09	0.71
overactivity at home	-0.11	0.08	0.10	-0.13	0.77	0.09
atten. problems at home	0.01	-0.18	0.12	0.30	0.66	0.34
impulsivity at home	0.18	0.15	0.19	0.14	0.66	-0.21
wets pants at school	0.93	0.09	0.01	-0.03	0.03	0.05
steals at school	-0.05	0.24	0.65	0.07	0.00	-0.37
poor concentration (school)	-0.08	0.23	0.08	0.86	0.12	0.04
poor hygiene (school)	0.66	0.10	0.28	0.36	-0.03	0.07
fidgety at school	-0.14	0.23	0.01	0.43	0.58	-0.05
short attention span at school	0.14	0.09	0.00	0.89	0.09	0.11
soils self at school	0.91	0.09	-0.09	-0.06	-0.05	0.06
bullies at school	-0.00	0.82	0.07	0.05	0.08	-0.10
lies at school	0.19	0.54	0.42	0.29	0.06	-0.22
fights at school	0.04	0.80	0.17	0.15	0.18	0.02
destructive at school	0.26	0.65	0.13	0.15	-0.06	0.13
defecates/urinates in public at school	0.52	0.48	-0.16	-0.03	0.01	0.27

4.4.9 Behavioural disturbance (parent and teacher report)

***Hypothesis**: PWS and HSS groups will be phenotypically similar in terms of behavioural disturbance, and distinct from the stressed group.*

4.4.9.1 Behaviour disturbance factors

Using the PCA analysis described above, six summary variables were created: externalising at school, general externalising, attention/overactivity problems at school, general attention/overactivity problems, encopresis/enuresis at home and finally encopresis/enuresis at school. These factors were derived from both parent and teacher report. Table 4.4.9.1 describes the group means for each variable.

Table 4.4.9.1: Behavioural disturbance factors (parent and teacher report): group means

variable	*HSS (n=25) mean (sd)*	*PWS (n=30) mean (sd)*	*stressed (n=25) mean (sd)*
externalising at school	2.84 (1.91)	2.96 (2.36)	4.03 (2.11)
general externalising	7.40 (2.90)	6.55 (3.29)	5.56 (3.01)
attention/activity probs at school	4.40 (2.25)	3.94 (1.82)	3.94 (1.69)
general attention/activity probs	5.16 (2.78)	3.64 (1.96)	5.56 (3.01)
enuresis/encopresis at home	2.84 (1.91)	2.87 (1.83)	1.12 (1.67)
enuresis/encopresis at school	4.01 (1.73)	4.39 (2.12)	3.61 (1.29)

Using IQ as a covariate, with group and sex entered as factors, ANOVA analyses were applied. The results from these analyses are presented in table 4.4.9.2. There were no sex or sex x group interaction effects. Enuresis/encopresis at home was the only group comparison to reach significance ($F = 5.60$, $p = 0.01$). A post hoc Sheffe test, with IQ regressed out, showed that both the PWS and HSS group were significantly more likely than the stressed children to show this behaviour at home. Further analysis suggests that, although their behaviour is comparable, the aetiology of the enuresis/encopresis in the PWS and HSS groups may be distinct. Of those children who showed encopresis or enuresis, 72.2% of the HSS group did so in order to cause an impact according to parental report (for example over furniture or belongings), as compared to 29.2% of children with PWS, and 36.4% in the stressed group. A chi square analysis of this distribution proved significant (Pearson value = 9.17, $df = 2$, $p = 0.01$). By examining the contribution that each cell makes to the final chi square value (see appendix 10) , it is evident that the HSS group are significantly more likely to soil themselves deliberately, in order to cause an impact, than either the stressed or PWS groups.

Table 4.4.9.2: Behavioural disturbance factors (parent and teacher reports): ANOVA analyses

variable	*source of variance (df) F value and significance*		
	group (df=2)	*sex (df=1)*	*group x sex (df=2)*
externalising at school	F = 2.19 p = 0.12	F = 0.04 p = 0.84	F = 0.14 p = 0.87
general externalising	F = 1.27 p = 0.29	F = 0.11 p = 0.75	F = 0.09 p = 0.92
attention/activity probs at school	F = 1.26 p = 0.29	F = 0.10 p = 0.75	F = 0.88 p = 0.42
general attention/ activity probs	F = 2.40 p = 0.10	F = 0.13 p = 0.72	F = 0.59 p = 0.56
enuresis/encopresis at home	F = 5.60 p = 0.01	F = 3.19 p = 0.08	F = 0.16 p = 0.85
enuresis/encopresis at school	F = 0.34 p = 0.72	F = 0.24 p = 0.88	F = 0.51 p = 0.60

Correlation with age:

With IQ held constant, correlations were explored between age and each of the behavioural disturbance variables. Across the whole sample, there were two significant relationships: a positive correlation with general externalising and age (r = 0.36, p > 0.01) and an inverse relationship with enuresis/encopresis at school and age (r = -0.30, p 0.01). School externalising (r = 0.15, p = 0.18), attention/activity problems at school (r = -0.03, p = 0.78), general attention/activity problems (r = 0.02, p = 0.88) and enuresis and encopresis at home (r = -0.07, p = 0.56) all had non-significant relationships with age. Correlations within each group showed a different pattern. These are described in table 4.4.9.3. The HSS group did not show any age related effects, while the PWS group were increasing less likely to show enuresis or encopresis at home as they get older, perhaps reflecting a maturation of muscle control. The stressed group were significantly more likely to demonstrate externalising problems as age increases.

Table 4.4.9.3: Behavioural disturbance correlation with age: within groups

	correlation with age		
variable	*HSS*	*PWS*	*stressed*
externalising at school	r = -0.02 p = 0.91	r = -0.10 p = 0.61	r = 0.49 p = 0.02
general externalising	r = 0.11 p = 0.62	r = 0.31 p = 0.10	r = 0.64 p < 0.00
attention/activity problems at school	r = 0.10 p = 0.64	r = -0.03 p = 0.87	r = -0.22 p = 0.30
general attention/activity problems at school	r = -0.13 p = 0.55	r = -0.03 p = 0.86	r = 0.13 p = 0.56
enuresis/encopresis at home	r = 0.33 p = 0.18	r = -0.44 p = 0.02	r = -0.07 p = 0.74
enuresis encopresis at school	r = -0.27 p = 0.20	r = 0.22 p = 0.24	r = 0.25 p = 0.25

Individual item comparisons:

4.4.9.2 sleep disturbance

A number of specific aspects of behaviour were examined using individual items from parent and teacher report. Group means for these items are described in table 4.4.9.4. Sleep disturbance showed a significant group effect (F = 3.56, p = 0.03). A post hoc analysis (Sheffe), taking IQ into account, showed that no two groups were significantly different from one another. Sex effects and interaction effects did not reach significance (F = 0.18, p = 0.68 and F = 0.08, p = 0.92 respectively).

Table 4.4.9.4: Behavioural disturbance individual items: group means

variable	*HSS (n =25) mean (sd)*	*PWS (n= 30) mean (sd)*	*stressed (n = 25) mean (sd)*
self-injurious behaviour	1.40 (1.32)	2.40 (1.13)	1.24 (1.39)
sleep disturbance	1.92 (1.15)	2.23 (1.16)	1.20 (1.22)
poor peer relations (parent report)	1.88 (1.33)	1.27 (1.26)	1.04 (1.21)
poor peer relations (teacher report)	0.52 (0.65)	0.41 (0.69)[4]	0.86 (0.89)[5]

The 'sleep' variable reflects degrees of sleep disturbance. A score of '3', indicates the greatest level of disturbance, describing children who 'roam' at night, playing, destroying items or , in some cases, stealing food . This rating identifies children who have disturbed sleep rhythm, and not simply sleep interruption through nightmares, sleep walking or intrusive thoughts, for example. With this distinction in

[4] data were unavailable for 2 cases
[5] data were unavailable for 3 cases

mind, the variable was analysed dichotomously, with those children who roamed at night compared against those who did not. 44% of the HSS group, 63 % of the PWS and 20% of the stressed group roamed at night. A 3x2 square was highly significant (Pearson chi square value = 10.40, $p < 0.00$). By examining the contribution that each groups' cells made towards the final chi square value, it is clear that the children with PWS are significantly more likely to show night roaming than the other groups. However, after subtracting the PWS group's chi square contribution from the final value, making 5.55, it remains significant at 0.05 (df = 1). This indicates that, in addition, the HSS group are significantly more likely to show night roaming than the stressed group.

4.4.9.3 Self-injury

There were no significant group ($F = 1.23$, $p = 0.30$), sex ($F = 0.53$, $p = 0.47$) or interaction effects ($F = 0.39$, $p = 0.68$) in terms of self injurious behaviour. Examination of the means (table 4.4.9.4) shows a tendency for the PWS group to have greater difficulties in this area. Without IQ as a covariate, the children with PWS are significantly different from both groups, but after controlling for IQ, this significance is not maintained.

4.4.9.4 Peer relationships

Peer relationships, as reported by parents ($F = 2.38$, $p = 0.10$) and teachers ($F = 0.21$, $p = 0.81$), did not differentiate the groups. According to the children themselves there was no group effect in terms of peer relationships or friendships (see 4.4.7). Sex effects (parent report: $F = 0.62$, $p = 0.43$ and teacher report: $F = 0.97$, $p = 0.33$) were not significant . Nor were the interaction effects according to both parents ($F = 0.78$, $p = 0.46$) and teachers ($F = 1.34$, $p = 0.27$). Table 4.4.9.4 describes the group means for each of these variables.

4.4.9.5 Attention, overactivity and impuisivity

Although the attention/overactivity problems variable did not differentiate the groups, given that children with PWS have been demonstrated to have a lower activity level than weight matched controls (Davies et al, 1992), the contribution of attention, impulsivity and activity respectively was explored. Group means are reported in table 4.4.9.5. Rather surprisingly, with IQ as a covariate, there were no group differences on parental or teacher reported activity levels and parent reports of impulsivity and attention deficits. These analyses are described in table 4.4.9.6.

Table 4.4.9.5: Attention, overactivity and impulsivity items : group means

variable	*HSS (n =25) mean (sd)*	*PWS (n= 30) mean (sd)*	*stressed (n = 25) mean (sd)*
attention problems	1.58 (0.88)	1.04 (0.58)	1.32 (0.80)
impulsivity	1.58 (0.83)	1.44 (0.80)	1.52 (0.71)
overactivity (parent report)	1.13 (0.99)	0.70 (0.70)	1.92 (2.17)
overactivity (teacher report)	0.88 (0.88)	0.41 (0.64)[6]	0.82 (0.80)[7]

Table 4.4.9.6: Attention, overactivity and impulsivity items :ANOVA analyses

variable	*source of variance (df) F value and significance*
	group (df=2)
attention problems	F= 2.40 p = 0.10
impulsivity	F = 0.20 p = 0.82
overactivity (parent report)	F = 1.71 p = 0.19
overactivity (teacher report)	F = 1.12 p = 0.33

4.4.9.6 Summary

The analyses do not support the hypothesis. 5 of 6 summary variables failed to distinguish the groups. The only identifying variable, enuresis/encopresis at home, which does potentially support the hypothesis was demonstrated to be distinct in origin in the PWS and HSS groups. In other words, though the PWS and HSS groups showed comparable behaviour, the reason for displaying such behaviour did not correspond, according to care-giver report. Sleep disturbance, defined as night roaming, analysed as a dichotomous variable, showed that children with PWS were significantly more likely to roam at night than the HSS or stressed children, but in addition, children with HSS were significantly more likely to night roam than the stressed group.

[6] data were unavailable for 2 cases
[7] data were unavailable for 3 cases

4.4.10. Care-giver reported psychosocial profile (CBCL, Achenbach.1991a)

***Hypothesis**: HSS and PWS groups will be similar in terms of parent reported psychosocial adjustment, and distinct from the stressed group.*

4.4.10.1 Population T scores

The Child Behaviour Checklist (CBCL, Achenbach, 1991) describes children's psychosocial adjustment, across a wide range of functioning. The group means for each population T score (standardised scores corrected for age and sex trends) are presented in table 4.4.10.1. Total problem scores are calculated from an amalgam of the internalising and externalising scores, which are in turn made from a number of the individual syndrome problem scores such as attention problems. Taking into account the systematic group differences in cognitive ability (see 4.4.1), IQ was covaried in each ANOVA analyses, with group and sex entered as factors. The results of these analyses are presented in table 4.4.10.2. No sex effects proved to be significant. There were significant group effects on the externalising score. A Sheffe post hoc test (at an alpha level of 0.05) showed the nature of this effect. The stressed group had significantly more externalising problems than either the PWS or the HSS group, according to parents. The same pattern existed in the aggressive behaviour scale, with the stressed group having relatively more poor adjustment in these areas than either the HSS or PWS groups. The stressed group also scored significantly higher on the anxious/depressed scale than the PWS group, but were not significantly different from the HSS group. The final group difference was in the thought problems scale. Using the Sheffe post hoc test (at $p = 0.05$) it was evident that children with PWS showed significantly more problems than the HSS group, but were not distinct from the stressed group.

Table 4.4.10.1: Population T scores: group means

Population T score	*HSS (n =17) mean (sd)*	*PWS (n= 28) mean (sd)*	*stressed (n= 18) mean (sd)*
total problems	65.29 (11.30)	66.96 (7.15)	70.22 (10.40)
internalising	60.29 (12.30)	57.79 (7.00)	63.89 (11.83)
externalising	61.00 (12.90)	61.64 (10.00)	70.94 (9.56)
withdrawn	62.47 (11.45)	61.28 (6.91)	61.55 (9.91)
somatic complaints	60.06 (8.68)	60.71 (8.27)	58.61 (8.43)
anxious/depressed	59.53 (11.39)	52.93 (4.14)	66.50 (14.70)
social problems	64.17 (9.19)	71.75 (9.24)	66.44 (13.10)
thought problems	60.94 (7.81)	69.21 (7.30)	63.22 (9.37)
attention problems	70.00 (11.71)	65.39 (9.27)	69.00 (13.10)
delinquent behaviour	62.76 (10.45)	59.96 (8.83)	68.94 (9.82)
aggressive behaviour	62.70 (11.26)	63.00 (10.13)	72.17 (11.19)
sex problems	54.17 (7.64)	55.13 (8.11)	55.89 (13.02)

Table 4.4.10.2: CBCL population T scores: ANOVA analyses

	source of variance (df) F value & significance		
Population T score	*group (df=2)*	*sex (df=1)*	*group x sex (df=2)*
total problems	F = 1.29 p = 0.28	F = 0.50 p = 0.82	F = 0.34 p = 0.72
internalising	F = 1.42 p = 0.25	F = 0.28 p = 0.60	F = 0.16 p = 0.85
externalising	F = 3.90 p = 0.03	F = 0.02 p = 0.88	F = 0.34 p = 0.71
withdrawn	F = 0.02 p = 0.98	F = 2.57 p = 0.11	F = 0.09 p = 0.91
somatic complaints	F = 0.18 p = 0.84	F = 0.26 p = 0.61	F = 0.29 p = 0.75
anxious/depressed	F = 5.39 p = 0.01	F >0.00 p = 0.95	F = 0.57 p = 0.57
social problems	F = 1.24 p = 0.30	F = 0.41 p = 0.52	F = 0.39 p = 0.68
thought problems	F = 3.37 p = 0.04	F = 1.89 p = 0.18	F = 0.63 p = 0.54
attention problems	F = 2.67 p = 0.08	F = 0.67 p = 0.42	F = 0.30 p = 0.74
delinquent behaviour	F = 2.57 p = 0.09	F = 0.01 p = 0.93	F = 1.12 p = 0.33
aggressive behaviour	F = 4.31 p = 0.02	F = 0.03 p = 0.87	F = 0.09 p = 0.92
sex problems	F = 0.81 p = 0.42	F = 1.28 p = 0.27	F = 4.88* p = 0.01

** since the main effects are not significant, this interaction will not be discussed*

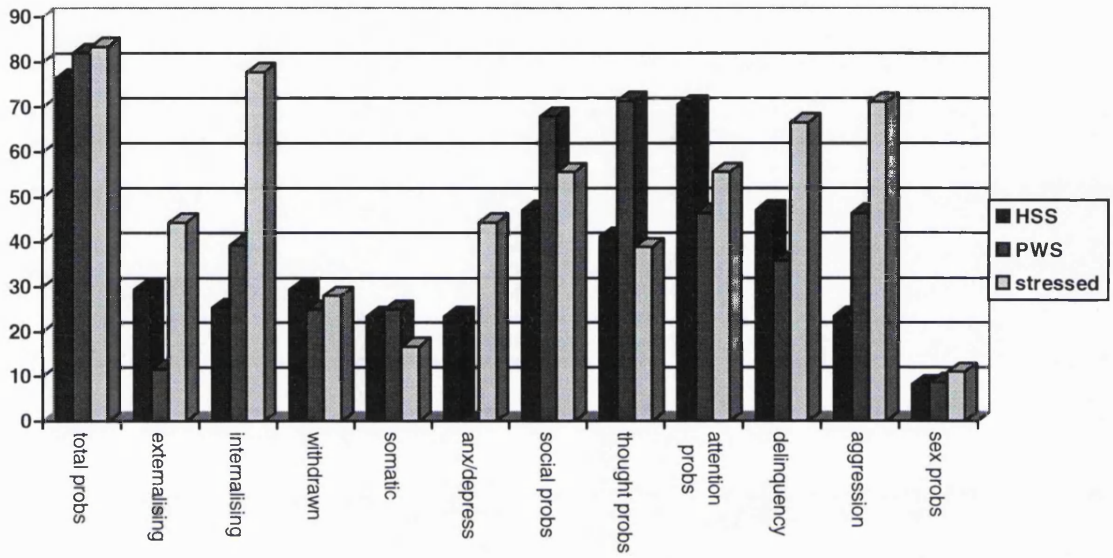
4.4.10.2 Clinical range scores

A T score of 67 on the syndrome problem scales indicates a borderline at which the CBCL referred clinical population score. Above 70 is more certainly within the clinical range. Scores of 67 or more discriminates reliably between referred and non-referred groups. For total problem scores the clinical cut-off score is 60 (Achenbach, 1991a).

The HSS group scored, on average, within the clinical range in the syndrome scores for attention problems and total problem scores. For the children in the PWS group, social problems, thought problems, and total problem scores all fell within the clinical range. The stressed group were above the clinical cut-off score in total problems, externalising,

attention problems, delinquent behaviour and aggressive behaviour sub-scale scores. Figure 4.4.10.1 describes the percentage of individual children in each group falling above the clinical cut-off score in each sub-scale score.

Figure 4.4.10.1: Clinical range scores: group percentages above the cut-off.



Correlations with age

With IQ regressed out, each T score scale was correlated with age. The correlations are described in table 4.4.10.3. Across the full sample, total problem score, internalising externalising, anxious/depressed, social problems, attention and delinquency all correlated significantly, and positively with age. When the correlations were performed within each group, a clear pattern emerged. Neither the HSS or the PWS group sub-scales showed any significant correlation with age but somatic complaints, anxious/depressed, attention problems and delinquent behaviour all correlated significantly and positively with age in the stressed group. Given these rather group specific age correlations, the ANOVA analyses described in table 4.4.10.2, were performed again with *both* age and IQ covaried. Significant contrasts in the externalising and anxious depressed scales were not maintained ($F = 2.37$, $p = 0.10$ and $F = 2.80$ $p = 0.70$ respectively) The significant group effect in thought problems ($F = 3.31$, $p = 0.04$) and aggressive behaviour ($F = 3.18$, $p = 0.05$) remained. All main sex effects were non-significant. It is feasible that two of the main effects reached significant due to the non-significant trend for the stressed children to be older (see 4.2.5.1) than the PWS and HSS groups.

Table 4.4.10.3: CBCL population T scores: correlation with ages, full sample and within groups

Population T score	*full sample*	*HSS*	*PWS*	*stressed*
total problems	r = 0.25 p = 0.05	r = 0.12 p = 0.65	r < -0.00 p = 0.99	r = 0.47 p = 0.06
internalising	r = 0.25 p = 0.05	r = 0.02 p = 0.93	r = 0.16 p = 0.40	r = 0.40 p = 0.11
externalising	r = 0.55 p = 0.05	r = 0.10 p = 0.69	r = -0.06 p = 0.77	r = 0.47 p = 0.06
withdrawn	r = -0.01 p = 0.91	r = -0.06 p = 0.81	r = 0.03 p = 0.88	r = 0.06 p = 0.81
somatic complaints	r = 0.11 p = 0.39	r = -0.15 p = 0.56	r = 0.13 p = 0.52	r = 0.49 p = 0.04
anxious/depressed	r = 0.36 p < 0.00	r = 0.04 p = 0.87	r = 0.24 p = 0.20	r = 0.48 p = 0.05
social problems	r = 0.25 p = 0.05	r = 0.25 p = 0.33	r = 0.19 p = 0.34	r = 0.41 p = 0.10
thought problems	r = -0.04 p = 0.77	r = 0.08 p = 0.75	r = -0.14 p = 0.49	r = 0.03 p = 0.91
attention problems	r = 0.27 p = 0.03	r = 0.27 p = 0.29	r = 0.03 p = 0.88	r = 0.48 p = 0.05
delinquent behaviour	r = 0.27 p = 0.03	r = 0.23 p = 0.37	r = -0.08 p = 0.68	r = 0.52 p = 0.03
aggressive behaviour	r = 0.19 p = 0.14	r = -0.16 p = 0.54	r = -0.04 p = 0.84	r = 0.41 p = 0.10
sex problems	r = -0.06 p = 0.71	r = 0.38 p = 0.22	r = 0.04 p = 0.86	r = -0.57 p = 0.14

4.4.10.3 Summary

The analyses largely fail to support the hypothesis, as in 8 of the 12 sub-scales, the group are indistinguishable and on a further sub-scale (thought problems), the HSS group was distinct from the PWS group but not from the stressed group. The stressed group showed significantly more psychosocial adjustment problems on two sub-scales and were, in fact, distinct from the PWS and HSS groups as hypothesised. However this does not support the idea of a specific phenotypic similarity in the HSS and PWS groups as comparative positive adjustment does not constitute a behavioural phenotype.

4.4.11 Teacher reported Psychosocial profile (TRF, Achenbach,1991b)

***Hypothesis**: HSS and PWS will be similar in terms of psychosocial adjustment, and distinct from the stressed group.*

4.4.11.1 Population T scores

The Teacher Report Form (TRF Achenbach, 1991b) is the parallel instrument to the CBCL, being a behavioural profile reported by teachers. As with the CBCL, the measure describes a wide range of functioning and provides standardised population T scores for comparison purposes. Table 4.4.11.1 shows the group means for each of the sub-scale scores. ANOVA analyses, with IQ covaried, were used. Group and sex were entered as factors. All post hoc comparisons were performed, holding IQ constant, rather than on 'raw' group means. There were two significant group differences, on the anxious/depressed and delinquent behaviour scales (see table 4.4.11.2). With a significance level of 0.05, post hoc Sheffe tests showed that on the anxious/depressed sub-scale, the stressed group showed significantly more disturbed behaviour than the PWS group . However, no two groups were significantly different from one another in the delinquency sub-scale score. There was one significant sex effect, with teachers reporting that girls across the full sample were exhibiting significantly more attention symptoms (64.72, sd 10.11) than did boys (60.72, sd 7.95). The TRF, like the CBCL is standardised with separate scores for boys and girls and so this may suggest that, as compared to the general population, the girls in our study exhibited proportionately more attention symptomology than the boys. None of the 2 way interactions reached significance.

Table 4.4.11.1: TRF population T scores: group means

Population T scale	*HSS (n =24) mean (sd)*	*PWS (n = 25) mean (sd)*	*stressed (n = 22) mean (sd)*
total problem score	60.88 (9.60)	64.68 (9.33)	65.95 (9.19)
internalising	56.21 (11.28)	59.64 (9.13)	61.59 (9.64)
externalising	59.83 (9.92)	63.23 (9.38)	67.23 (9.38)
withdrawn	58.58 (10.49)	58.80 (6.92)	57.68 (6.31)
somatic complaints	56.13 (9.11)	62.12 (7.98)	55.45 (6.80)
anxious/depressed	57.79 (7.08)	57.16 (8.73)	64.36 (10.27)
social problems	62.17 (5.74)	62.56 (7.36)	67.18 (9.48)
thought problems	57.92 (9.38)	61.52 (10.19)	58.73 (10.84)
attention problems	61.46 (9.77)	61.16 (7.86)	61.04 (8.38)
delinquent behaviour	59.21 (7.06)	60.00 (8.46)	64.95 (8.23)
aggressive behaviour	60.83 (9.48)	64.68 (10.67)	67.95 (11.49)

Table 4.4.11.2: TRF Population T score: ANOVA analyses

	source of variance (df) F value & significance		
Population T scale	*group (df=2)*	*sex (df=1)*	*sex x group (df = 2)*
total problem score	F = 0.60 p = 0.56	F = 3.22 p = 0.08	F = 0.75 p = 0.48
internalising	F = 0.82 p = 0.44	F = 1.36 p = 0.24	F = 0.23 p = 0.80
externalising	F = 1.44 p = 0.25	F = 3.56 p = 0.06	F = 0.66 p = 0.52
withdrawn	F = 0.08 p = 0.93	F = 0.22 p = 0.64	F = 0.01 p = 0.99
somatic complaints	F = 3.01 p = 0.06	F = 1.89 p = 0.18	F = 2.90 p = 0.06
anxious/depressed	F = 3.66 p = 0.03	F = 1.59 p = 0.21	F = 0.54 p = 0.59
social problems	F = 1.96 p = 0.15	F = 0.26 p = 0.61	F = 1.23 p = 0.30
thought problems	F = 0.52 p = 0.60	F = 0.02 p = 0.88	F = 0.83 p = 0.44
attention problems	F = 1.27 p = 0.29	F = 4.69 p = 0.03	F = 1.36 p = 0.26
delinquent behaviour	F = 3.48 p = 0.04	F = 1.73 p = 0.19	F =0.14 p = 0.87
aggressive behaviour	F = 1.12 p = 0.33	F = 2.68 p = 0.11	F = 0.70 p = 0.50

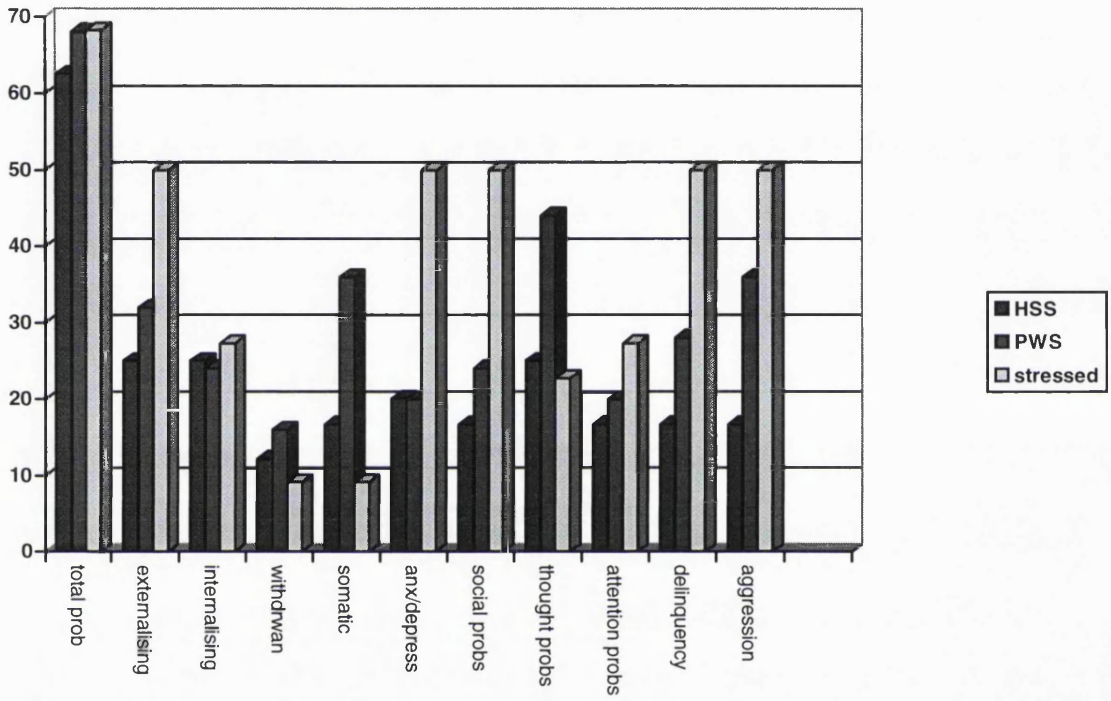
4.4.11.2 Clinical range scores

The TRF population T scores are distributed so that a score of between 67 and 70 on the syndrome problem sub-scale fall into the clinical borderline range. Scores above 70 are regarded as being more certainly within the clinical range. Scores above 67 describe relatively disturbed behaviour, as the cut-off distinguishes between referred and non-referred samples (Achenbach, 1991b). For the total problem score, the clinical cut-off score is 60.

Teachers reported that none of the PWS or HSS group children were within the clinical range for any of the syndrome sub-scales but both groups were in the clinical range for total problem scores. Externalising, social problems and aggressive behaviour sub-scale scores, in addition to total problem score, reached the clinical range in the stressed

group. As with the CBCL measure (see 4.4.10), the stressed children were comparatively more maladjusted than either the HSS or PWS group children relative to the general population. Figure 4.4.11.1 describes the proportion of children within each group falling *above* the clinical cut-off for each group.

Figure 4.4.11.1: TRF clinical range scores: group percentages above the cut-off.



Correlations with age:

Although the TRF is standardised across age groups, in order to explore the data as extensively as possible, each sub-scale (with IQ regressed out) was correlated with age. These data are presented in table 4.4.11.3. Across the full sample, total problems, externalising, anxious/depressed , delinquent and aggressive behaviour sub-scale scores all correlated positively and significantly with age. In other words, as children got older, the reported severity of their symptoms increased. A similar pattern of significant positive correlation in the PWS group (internalising and anxious/depressed) and stressed group (total problems, internalising, anxious/depressed, thought problems and delinquent behaviour) emerged. However, the only age related trend in the HSS group was negative, with reported social problems decreasing with age, according to teachers.

As with the CBCL data, bearing these age related relationships in mind, the ANOVA analyses were repeated with age covaried in addition to IQ, and the significant group contrasts that had been evident in delinquent behaviour were not maintained (F = 0.44, p = 0.65) nor were there any sex (F = 2.83, p = 0.10) or interaction effects (0.98, p = 0.38). The significant group effect also disappeared in the anxious/depressed scale (F = 1.50, p = 0.23), the sex (F = 1.75, p = 0.19) and interaction effects (F = 0.39, p = 0.68) remained non-significant.

Table 4.4.11.3: TRF Population T scores: correlation with ages, full sample and within groups

Population T score	*full sample*	*HSS*	*PWS*	*stressed*
total problems	r = 0.25 p = 0.04	r = -0.03 p = 0.88	r = 0.25 p = 0.22	r = 0.47 p = 0.03
internalising	r = 0.20 p = 0.09	r = -0.19 p = 0.38	r = 0.39 p = 0.05	r = 0.47 p = 0.03
externalising	r = 0.24 p = 0.04	r = 0.08 p = 0.73	r = 0.10 p = 0.65	r = 0.40 p = 0.07
withdrawn	r = 0.05 p = 0.70	r = -0.14 p = 0.52	r = 0.24 p = 0.25	r = 0.30 p = 0.19
somatic complaints	r = -0.07 p = 0.57	r = -0.16 p = 0.45	r = 0.02 p = 0.92	r = 019 p = 0.41
anxious/depressed	r = 0.36 p <0.00	p = -0.12 p = 0.58	r = 0.48 p = 0.02	r = 0.47 p = 0.03
social problems	r = 0.19 p = 0.12	r = -0.41 p = 0.05	r = 0.31 p = 0.13	r = 0.35 p = 0.12
thought problems	r = 0.12 p = 0.35	r = -0.13 p = 0.55	r = 0.08 p = 0.71	r = 0.46 p = 0.03
attention problems	r = 0.13 p = 0.28	r = 0.02 p = 0.92	r = 0.26 p = 0.21	r = 0.11 p = 0.63
delinquent behaviour	r = 0.30 p = 0.01	r = 0.19 p = 0.40	r = -0.04 p = 0.86	r = 0.52 p = 0.02
aggressive behaviour	r = 0.25 p = 0.04	r = 0.04 p = 0.84	r = 0.18 p = 0.38	r = 0.35 p = 0.12

4.4.11.3 Summary

The majority of sub-scale comparisons showed that each of the groups were indistinguishable from one another. The analyses does not, therefore, support the hypothesis. There was no evidence of a characteristic psychosocial adjustment pattern, according to teacher report, in the HSS and PWS groups as compared to the stressed children. In terms of anxious/depressed behaviour, the stressed group *were* independent from the HSS and PWS group but on the basis of their relatively poor adjustment in comparison to the other groups.

4.4.12 A comparison of disturbances at home and school

Hypothesis: *HSS and PWS groups will show equivalent degrees of psychosocial and appetite disturbance at home and at school.*

In order to test this hypothesis thoroughly, comparisons between reported behaviour at home and at school were made in variety of domains, not just those shown to be specific to the HSS syndrome. There is a potential confounding factor in these comparisons, as behaviour in each context is reported by different individuals with potentially different criteria for problematic behaviour. Therefore, it was considered appropriate to examine a wide range of psychosocial factors in order to explore, within the limitations of the data, any systematic differences in parent and teacher report or in true context specific behaviour patterns. If there were a systematic bias, this should be evident for all aspects of behaviour and not just hyperphagia.

If parental and teacher accounts of hyperphagia for children with PWS were consistent across contexts, but there was a discrepancy between parent and teachers' reports of hyperphagia in the HSS group, this would raise questions about the validity of hyperphagia as a behavioural phenotype in HSS. If, however the reports of hyperphagia are inconsistent at home and school in the PWS group, it would seem acceptable for there to be inconsistency in the HSS group too.

4.4.12.1 Psychosocial disturbance

Teacher and parent reports (Achenbach sub-scales)

Using a series of repeated measures ANOVA models, each sub-scale in the CBCL was tested against the equivalent sub-scale in the TRF. In these set of analyses, IQ was not covaried, as it was not considered a confounding variable in examination of behaviour *consistency*, as opposed to severity.

Table 4.4.12.1 describes the group means, and the full sample means for each of the sub-scales, and the means for each group (note the TRF does not provide a sex problems sub-scale, and so this sub-scale could not be discussed in terms of home and school consistency*).* A summary of the ANOVA analyses in table 4.4.12.2, shows that across the full sample, there were significant differences in home and school reported behaviour on the total problem score, social problems, thought problems and attention problems sub-scale. Examination of the means shows that in each case, caregivers

reported a significantly greater degree of adjustment difficulty than teachers. This may be due to a true systematic difference in behaviour at home or school, or it may be an artefact of the reporter. Teachers may, for example be reluctant to describe problem behaviour. There was one group x context interaction, in which the PWS group were described as having a significantly greater degree of disparity between home and school reports than either of the other groups. The PWS group children are reported by caregivers as having significantly more social problems at home than are reported by teachers at school, in comparison to either the HSS or stressed groups.

Table 4.4.12.1: Population T scores in the CBCL and TRF: full sample and group means

	Child Behaviour Checklist				***Teacher Report Form***			
Population T score	*full sample (n=63) mean (sd))*	*HSS (n =17) mean (sd)*	*PWS (n= 28) mean (sd)*	*stressed (n= 18) mean (sd)*	*full sample (n=71) mean (sd))*	*HSS (n =24) mean (sd)*	*PWS (n = 25) mean (sd)*	*stressed (n = 22) mean (sd)*
total problems	67.44 (9.40)	65.29 (11.30)	66.96 (7.15)	70.22 (10.40)	63.79 (9.49)	60.88 (9.60)	64.68 (9.33)	65.95 (9.19)
internalising	60.21 (10.26)	60.29 (12.30)	57.79 (7.00)	63.89 (11.83)	59.08 (10.16)	56.21 (11.28)	59.64 (9.13)	61.59 (9.64)
externalising	64.13 (11.43)	61.00 (12.90)	61.64 (10.00)	70.94 (9.56)	63.25 (10.08)	59.83 (9.92)	63.23 (9.38)	67.23 (9.38)
withdrawn	61.68 (9.04)	62.47 (11.45)	61.28 (6.91)	61.55 (9.91)	58.38 (8.05)	58.58 (10.49)	58.80 (6.92)	57.68 (6.31)
somatic complaints	59.94 (8.34)	60.06 (8.68)	60.71 (8.27)	58.61 (8.43)	58.03 (8.50)	56.13 (9.11)	62.12 (7.98)	55.45 (6.80)
anxious/depressed	58.59 (11.53)	59.53 (11.39)	52.93 (4.14)	66.50 (14.70)	59.61 (9.20)	57.79 (7.08)	57.16 (8.73)	64.36 (10.27)
social problems	68.19 (10.82)	64.17 (9.19)	71.75 (9.24)	66.44 (13.10)	63.86 (7.84)	62.17 (5.74)	62.56 (7.36)	67.18 (9.48)
thought problems	65.27 (8.74)	60.94 (7.81)	69.21 (7.30)	63.22 (9.37)	59.44 (10.11)	57.92 (9.38)	61.52 (10.19)	58.73 (10.84)
attention problems	67.67 (11.14)	70.00 (11.71)	65.39 (9.27)	69.00 (13.10)	61.23 (8.58)	61.46 (9.77)	61.16 (7.86)	61.04 (8.38)
delinquent behav.	63.29 (10.14)	62.76 (10.45)	59.96 (8.83)	68.94 (9.82)	61.27 (8.22)	59.21 (7.06)	60.00 (8.46)	64.95 (8.23)
aggressive behav.	65.54 (11.38)	62.70 (11.26)	63.00 (10.13)	72.17 (11.19)	64.39 (10.79)	60.83 (9.48)	64.68 (10.67)	67.95 (11.49)

Table 4.4.12.2: Population T scores in the CBCL and TRF: Repeated measures ANOVA analyses.

	Source of variance (df) F value and significance		
variable	*group* (df = 2)	*context (home and school)* (df = 1)	*group x context* (df = 2)
total problems	F = 1.70 p = 0.19	F = 5.75 p = 0.02	F = 0.37 p = 0.70
internalising	F = 1.35 p = 0.27	F = 0.28 p = 0.60	F = 0.81 p = 0.45
externalising	F = 3.86 p = 0.03	F = 0.53 p = 0.47	F = 1.40 p = 0.26
withdrawn	F = 0.19 p = 0.83	F = 2.67 p = 0.11	F = 0.06 p = 0.94
somatic complaints	F = 3.08 p = 0.05	F = 1.75 p = 0.19	F = 0.80 p = 0.46
anxious/depressed	F = 7.91 p <0.01	F = 0.00 p = 0.98	F = 2.95 p = 0.06
social problems	F = 1.38 p = 0.26	F = 7.28 p = 0.01	F = 3.23 p = 0.05
thought problems	F = 0.40 p = 0.25	F = 6.72 p = 0.01	F = 1.02 p = 0.37
attention problems	F = 0.57 p = 0.57	F = 18.60 p <0.00	F = 1.29 p = 0.28
delinquent behaviour	F = 3.95 p = 0.03	F = 3.00 p = 0.09	F = 0.72 p = 0.49
aggressive behaviour	F = 3.83 p = 0.03	F = 0.78 p = 0.38	F = 1.42 p = 0.25

Correlations between parent and teacher report in the Achenbach scales:

The correlations between parent and teacher reports in each of the sub-scales for individual children, across the full sample and within each group are reported in table 4.4.12.3. For individual children, across the full sample, there were significant positive correlations between parents' and teachers' reports for the total problems, externalising and internalising sub-scales. Correlations within groups do not correspond with one another as frequently as across the full sample. The individual sub-scales, across the full sample were largely consistent between parent and teacher reports. As before, within groups, there was greater discrepancy between parent and teacher reports within groups, particularly in the HSS group.

Table 4.4.12.3: Parent and teacher report correlations: TRF and CBCL

sub-scale	*full sample*	*HSS*	*PWS*	*stressed*
total problems	r = 0.45 p < 0.00	r = 0.27 p = 0.31	r = 0.52 p = 0.01	r = 0.54 p = 0.03
internalising	r = 0.39 p < 0.00	r = 0.18 r = 0.49	r = 0.58 p < 0.00	r = 0.44 p = 0.09
externalising	r = 0.56 p < 0.00	r = 0.51 p = 0.04	r = 0.49 p = 0.02	r = 0.67 p < 0.00
withdrawn	r = 0.39 p < 0.00	r = 0.42 p = 0.11	r = 0.52 p = 0.01	r = 0.25 p = 0.34
somatic complaints	r = 0.18 p = 0.19	r = 0.20 p = 0.46	r = 0.20 p = 0.36	r = -0.02 p = 0.94
anxious/depressed	r = 0.55 p < 0.00	r = 0.58 p = 0.02	r = 0.43 p = 0.40	r = 0.53 p = 0.03
social problems	r = 0.36 p < 0.00	r = 0.06 p = 0.81	r = 0.44 p = 0.04	r = 0.48 p = 0.06
thought problems	r = 0.29 p = 0.03	r = -0.03 p = 0.89	r = 0.23 p = 0.30	r = 0.48 p = 0.06
attention problems	r = 0.43 p < 0.00	r = 0.43 p = 0.10	r = 0.46 p = 0.03	r = 0.46 p = 0.07
delinquent behaviour	r = 0.46 p < 0.00	r = 0.08 p = 0.76	r = 0.41 p = 0.05	r = 0.68 p < 0.00
aggressive behaviour	r = 0.41 p < 0.00	r = 0.21 p = 0.44	r = 0.34 p = 0.10	r = 0.53 p = 0.04

4.4.12.2 Hyperphagia

Home and school reported hyperphagia correlations:

As the home and school hyperphagia were reports were measured on different scales, only within child correlations, rather than group analysis were performed. The parent reported hyperphagia variables were summed and correlated with the school reported hyperphagia variables.

Across the full sample, hyperphagia, as reported by care-givers and teachers correlated highly (r = 0.59, p = < 0.00) . Within each group, this significant correlation was maintained in the HSS group (r = 0.42 p = 0.04) the PWS group (r = 0.49, p = 0.01) but not in the stressed group (r = 0.23, p = 0.27).

4.4.12.3 Summary

These analyses can support the hypothesis that PWS and HSS have comparable consistency in the degree of hyperphagia reported at home and school. Evidence from the correlations indicates that there is correspondence across the home and school contexts for each child in the PWS and the HSS groups. Further, analysis of the parent and teacher reports of adjustment using the parallel forms of the Achenbach measure, suggests that although there is a tendency for care-givers to report rather more problematic behaviours than teachers, but this tendency, largely, is maintained across groups.

4.4.13 Dysmorphology

***Hypothesis**: Children with HSS have a characteristic 'PWS-like' facies.*

Children in the HSS and PWS groups only were photographed. None of the stressed children were photographed. Given the circumstances in which many of the stressed group were living, it was considered inappropriate to ask families permission to photograph their children without there being a clinical justification to do so. 30 children with PWS and 24 children with HSS were presented of whom 2 were affected siblings of two index children.

A random blind presentation of colour slides was presented to two experienced dysmorphologists from the Mothercare Clinical Genetics Unit, at the Institute of Child Health. The dysmorphologists, raters 1 and 2, were informed that they would be presented with a series of children identified as having one of two syndromes. One syndrome, condition A, was well recognised, while condition B was an as yet unidentified genetic condition (condition A was PWS and B was HSS). The raters were then asked to classify each child into one of two groups. After viewing a number of slides, both raters identified condition A as PWS.

Only one HSS affected child was identified wrongly as having PWS by both raters and so 96% of the HSS group were identified as being non-PWS. Using a binomial test, this is significantly greater than chance ($p < 0.00$). 87% of children in the PWS group were identified correctly as having PWS by rater 1 and 94% by rater 2. One PWS child was wrongly identified as being non-PWS by both raters. Rater 2 misclassified two other PWS children as being non-PWS and rater 1, a further child.

The raters commented that obesity was often used as a cue to identifying PWS in children who did not have the characteristic facies. Children described as having the characteristic PWS face often have almond shaped eyes, a down turned mouth and a disproportionately narrow forehead. (Holm et al, 1993).

4.4.13.1 Summary

The hypothesis cannot be supported. Photographic evidence suggests that the children with HSS can be visually distinguished from the PWS group. Further, both dysmorphologists suggested that the children with HSS were not dysmorphic. In order to confirm objectively that HSS is not associated with a characteristic face, further testing would be required, comparing children with HSS to a normal comparison group .

4.5 Section C: The siblings

4.5.1 Familial Aggregation

***Hypothesis**: HSS shows familial aggregation:*

In order to test this hypothesis, the siblings of each index child were assessed using the HSS sibling check-list. Index children were not included in the analyses. Siblings were assigned as either affected or unaffected using the HSS diagnostic algorithm. Table 4.5.1.1 documents the total number of full, half and unrelated siblings assessed. A small number of siblings were not assessed, either because they fell outside the appropriate age of assessment, didn't wish to participate or because they were not living in the index child's household. Within this sample one pair of identical male twins were affected, one of these twins being the index child. Another pair of female identical twins were affected but in this case, they were the twin sisters of the index child. There were another set of male identical twins who were siblings of a further HSS proband, neither boy was affected. Only one half sibling of an HSS proband was affected. This sibling shared the same mother with the proband, and their fathers were brothers. Figure 4.5.1.1 describes the distribution of familial cases in the HSS group.

Anthropometric data

Anthropometric data were gathered for full HSS siblings only[1]. Parental report was employed for the remaining comparison group siblings. One stressed index child's sibling was measured, this case is described further below.

Using a multiple linear regression, described further below, we compared the heights of siblings affected, with those unaffected in the HSS group only. The criteria for short stature were broadened slightly in the sibling group, so children below the 10th centile were regarded as short. Family group and affected status together were significant predictors of height ($F = 8.99$, $p < 0.00$). By examining the Beta weights it is clear that though family group does contribute to height (Beta = 0.26, $T = 2.10$, $p = 0.04$), affected status is a stronger predictor of height (Beta = -0.42, $T = -3.44$, $p < 0.00$). Affected children were significantly shorter (-2.42 sds, sd 1.15) than their unaffected siblings (-0.07 sds, sd 2.30). This is slightly circular analyses, as affected

[1] data were unavailable for 32% of unaffected siblings

siblings are selected because they are short, but it is important because it demonstrates that hyperphagia predicts short stature within families in which there is an HSS affected child. It is important to note that some non-hyperphagic siblings were short (three had heights below 2 sds) and the group mean of unaffected full siblings is slightly below the population mean, but largely hyperphagia predicts short stature.

Figure 4.5.1.1: Distribution of affected siblings in HSS families - index children excluded

family	***affected*** *full siblings*	*unaffected full siblings*	***affected*** *half siblings*	*unaffected half siblings*
1	2	0	0	1
2	0	2	0	1
3	1	0	0	0
4	0	0	0	1
5	2	0	0	0
6	0	0	0	2
7	0	1	0	0
8	0	1	0	1
9	0	0	0	0
10	1	0	0	0
11	1	0	0	2
12	0	1	0	0
13	0	0	0	0
14	3 (twins +1)	2	0	0
15	1	0	0	0
16	1 (twin)	1	0	1
17	0	2	0	0
18	0	1	0	0
19	0	0	0	1
20	1	2 (twins)	0	0
21	0	2	0	0
22	0	0	1*	2
23	0	1	0	0
24	0	1	0	0
25	1	0	0	1

** this child shared the same mother with the proband, and their fathers were brothers.*

Table 4.5.1.1: Full, half and unrelated siblings assessed - index children excluded

	HSS		*PWS*		*stressed*	
sibling type	assessed	affected	assessed	affected	assessed	affected
full	30	13	29	0	19	0
half	14	1*	0	0	6	0
unrelated	0	0	0	0	3	0

** this child shared the same mother with the proband, and their fathers were brothers*

In order to test the sibling concordance hypothesis statistically, the sibling nearest in age to the index child was identified. A Pearson chi square analysis (table 4.5.1.2) shows that there is a significantly greater likelihood that siblings of HSS probands exhibit the phenotype when compared to the comparison groups' siblings.

Table 4.5.1.2: Nearest age siblings: chi square analysis: affected status by sibling group

analysis	*value*	*df*	*significance*
Pearson chi square	17.45	2	< 0.000

None of the siblings of PWS index children fitted the HSS diagnostic algorithm. This would suggest that hyperphagic behaviour is not mimicked by siblings in PWS households. It may follow, therefore that the 'affected' HSS group siblings are not simply imitating the HSS proband in terms of their food related behaviour.

One stressed index child and his full sibling fitted the diagnostic algorithm in terms of their hyperphagic behaviour only. This comparison sibling was assessed anthropometrically rather than relying on parental report, because she showed the behavioural aspect of the HSS phenotype. Neither the stressed index child nor his sibling were of short stature, being on the 75th centile and 50th centile for height respectively, and therefore were identified as unaffected. None of the other comparison siblings assessed were hyperphagic as defined in the HSS diagnostic algorithm.

Sex ratio:

There was no significant sex difference in the affected as compared to the unaffected siblings (index children excluded). Pearson chi square value = 0.74, df = 1, p = 0.78. With 29% of male and 33 % of female siblings being affected. This non-significant result was maintained if full siblings only were included in the analysis with 36% of male and 50% of female siblings being affected (chi square = 0.62, df = 1, p = 0.43).

4.5.1.1 Summary

This analysis supports the hypothesis that there is familial aggregation in HSS group sibships. There were significantly more siblings who fitted the HSS diagnostic algorithm in the HSS sibling group as compared to the siblings in the other groups.

4.5.2 Independent Indicators of HSS

***Hypothesis**: HSS is a distinct syndrome with independent indicators:*

A sub-sample of HSS families in which there was at least one affected and one unaffected child were selected. Using three independent indicators, cognitive ability, psychosocial adjustment and birthweight, we tested the hypothesis that children affected with the condition would be significantly distinct from their unaffected siblings.

A series of multiple linear regression equations were used to test the hypotheses. Two predictor variables were entered simultaneously. First affected status, whether the child was affected or unaffected. Second, family group was entered as a dummy variable so each sibship was assigned a number. In other words, the Smith family was labelled number 1, Jones, number 2 and so on. In this way intra-familial correlation was controlled. The sibship from which each child comes may contribute to the differences between affected and unaffected siblings because of shared environmental influences and genetic moderating influences independent of HSS. An alternative method involved analysing the data pair-wise with only one affected and one unaffected child per sibship but would have meant losing a portion of the data. The multiple linear regression method allowed maximal use of the data available.

4.5.2.1 Cognitive ability

***Hypothesis**: Affected siblings will demonstrate poorer cognitive abilities than unaffected siblings.*

Using full scale IQ as a dependent variable and the predictor variables described above multiple linear regressions were performed. Both predictor variables together explained 21% of the variance (R^2 = 0.21, F = 5.80. p = 0.005). The Beta weights explain the contribution that each predictor variable makes independently. Table 4.5.2.1. shows that the Beta weight associated with affected status is highly significant, indicating that affected status predicts cognitive ability. The Beta weight associated with family group is insignificant showing that the sibship from which each child came did not contribute to the effect. The direction of the effect is evident in the mean IQ scores with affected children (n = 36) mean IQ of 78.25 (sd 16.74) and unaffected siblings (n=11) with a mean IQ score of 95.63 (sd 11.12).

Repeating the same analysis with performance IQ as a dependent variable, a similar pattern emerges (see table 4.5.2.1.) with affected children having a mean performance IQ score of 79.28 (sd 21.01) and their unaffected siblings scoring 106.25 (sd 13.69). The F value for verbal IQ was insignificant (F = 2.25, p = 0.12), though the means suggest a trend in the hypothesised direction (affected siblings' mean verbal IQ was 75.20 (sd 19.38) as compared with unaffected siblings' verbal IQ of 87.81 (sd 14.88).

Table 4.5.2.1: Multiple linear regression: Full scale IQ, verbal IQ and performance IQ.

dependant variable	*affected status*			*family group*		
	Beta	*T*	*p*	*Beta*	*T*	*p*
IQ (full scale)	-0.46	-3.26	0.002	0.06	0.51	0.62
Performance IQ	-0.54	-4.18	<0.000	-0.09	-0.71	0.48

This analyses supports the hypothesis that affected children show poorer cognitive abilities in terms of full scale and performance IQ.

4.5.2.2 Psychosocial adjustment

Hypothesis: *affected children have greater adjustment difficulties than their unaffected siblings.*

We used the same analysis as described above to investigate various dimensions of psychosocial adjustment. CBCL population T scores were used in all analyses. For total problem score, both predictor variables explained 47% of the variance (R^2 = 0.47, F= 13.69, p < 0.000), with a significant Beta for affected status (p < 0.000) and a non-significant Beta for family group (p = 0.62). The finding held for internalising, externalising, withdrawn, social problems, thought problems, attention problems, delinquency problems and aggressive behaviour sub-scales (see table 4.5.2.2.). The R^2 was not significant for the remainder of sub-scales: somatic complaints (F = 2.55, p = 0.09), anxious/depressed problems (F = 2.47 p = 0.10) and sexual problem sub-scales (F = 1.70 p = 0.21).

Table 4.5.2.2.: Multiple Linear Regression: CBCL Population T scores.

dependant variable				*affected status*			*family group*		
	R^2	*F*	*p*	*Beta*	*T*	*p*	*Beta*	*T*	*p*
total prob. score	0.47	13.70	>0.000	0.69	5.21	>0.000	0.06	0.49	0.62
externalising	0.30	6.66	0.003	0.53	3.47	0.002	-0.69	-0.45	0.65
internalising	0.34	7.83	0.002	0.59	3.95	>0.000	0.14	0.91	0.37
withdrawn	0.24	4.88	0.014	0.50	3.11	0.004	0.05	0.31	0.76
social problems	0.20	3.84	0.032	0.45	2.76	0.010	0.04	0.23	0.82
thought problems	0.29	6.35	0.005	0.54	3.51	0.001	0.19	1.25	0.22
attention problems	0.42	11.01	>0.000	0.65	4.70	>0.000	0.12	0.90	0.38
delinquency	0.23	4.65	0.020	0.49	3.04	0.005	0.05	0.31	0.76
aggressive behav.	0.24	4.97	0.013	0.45	2.87	0.007	-0.12	-0.76	0.45

In all cases (see table 4.5.2.3) affected children demonstrated greater adjustment problems than their unaffected siblings according to care-giver report. The non-significant trend continued in this direction in the sub-scales in which there were no significant differences between affected and unaffected siblings. It should be noted that with the exception of attention problems and perhaps total problem score, the mean T score for affected children is not in the clinical or clinical border-line range defined by Achenbach (1991a and b). This significant result should be viewed as indicating poor adjustment problems relative to unaffected family members rather than in comparison to the general population. Further, it is important to note that only 2 of the 113 items that feed into these scales are appetite related, and therefore are independent of the diagnostic algorithm.

Table 4.5.2.3.: CBCL Population T scores: sibling affected status means

sub-scale	*affected siblings (n=23) mean (sd)*	*unaffected siblings(n=11) mean (sd)*
total problem score	66.30 (10.85)	44.36 (12.38)
externalising	63.70 (12.64)	47.18 (11.46)
internalising	60.91 (11.76)	44.27 (11.71)
withdrawn	62.30 (10.21)	51.91 (5.41)
somatic complaints	60.61 (9.06)	54.91 (5.91)
anxious/depressed	59.91 (10.99)	52.09 (5.66)
social problems	63.65 (10.08)	54.09 (7.27)
thought problems	62.13 (7.31)	53.27 (7.28)
attention problems	69.39 (11.95)	52.09 (4.41)
delinquent behaviour	65.43 (11.11)	54.36 (6.04)
aggressive behaviour	64.48 (11.67)	53.18 (4.51)
sex problems	55.47 (9.28)	51.55 (4.66)

The hypothesis that HSS affected children would show relatively poor psychosocial adjustment in comparison to their unaffected siblings is largely supported by these analyses.

4.5.2.3 Birthweight

***Hypothesis**: Affected children will have a lower birthweight than their unaffected siblings.*

Using the multiple linear regression equation described above, R^2 was insignificant for birth weight ($F = 1.31$, $p = 0.29$), although there was a non-significant trend indicating affected children tended to have a lower birthweight (97.85 ounces, sd 30.41, n = 20) than unaffected children (118.40 ounces, sd 19.38, n = 5). The numbers in this analyses are so small, that power is decreased , increasing the possibility of a type II error.

We cannot support the hypothesis that HSS affected children have lower birthweights than unaffected children.

4.5.2.4 Summary

Siblings affected with HSS have relatively poor performance and full scale IQ in comparison to their unaffected siblings. Further affected siblings have relatively poor psychosocail adjustment in 9 of 12 psychosocial domains. However birthweight was not significantly different between affected and unaffected siblings

4.6 Section D: molecular genetics

***Hypothesis**: The major locus associated with HSS coinherits with the locus associated with PWS at 15q11-13.*

This hypothesis was explored using two techniques; methylation status testing and sibling pair linkage analysis.

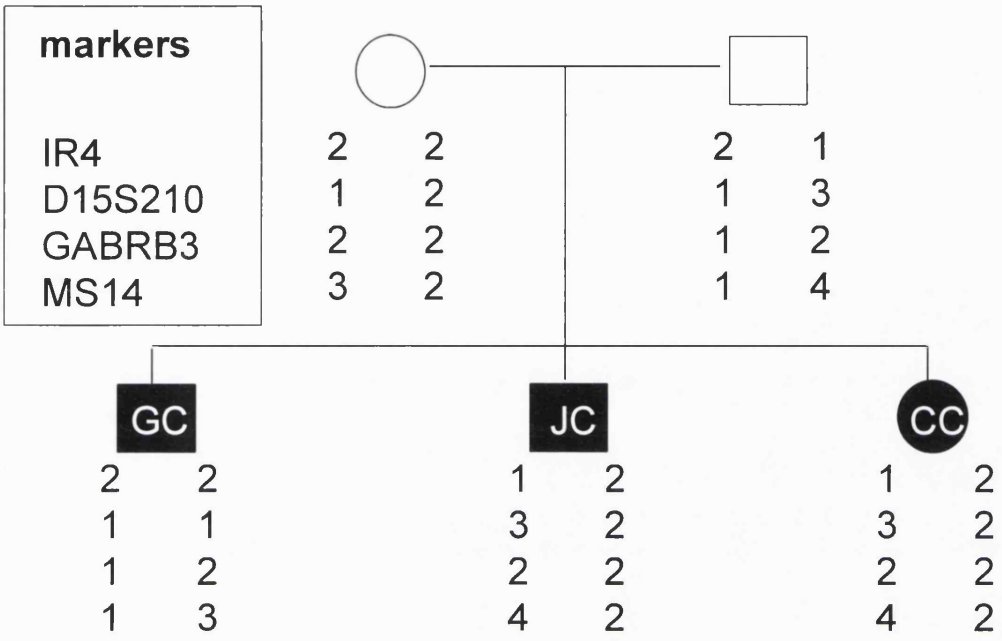
4.6.1 Methylation status testing

14 children affected with HSS were tested using the methylation status test described in 3.5 (Dittrich et al, 1992 and Buiting et al, 1994). After 14 HSS affected children had been tested, it was considered unnecessary to test any further cases as the methylation technique is so sensitive. Within this sample, there was one pair of affected siblings. Methylation testing does not necessarily require bloods from family members other than the index child. All fourteen children with HSS showed a normal methylation pattern at 15q11-13. In other words, all had one allele derived paternally and one derived maternally as one would expect in normal individuals who do not have PWS.

4.6.2 Sibling pair linkage analysis

Two family pedigrees were tested using four marker probes (Mutirangura et al, 1993) across the PWS regions, as described in 3.5 . In family C, DNA was available from both biological parents and all three affected full siblings. DNA was not available from a further unaffected half sibling. The pattern of allelic inheritance is described below in figure 4.6.2.1. Where parents have two alleles of the same type or both parents share the same type of allele, it is not possible to confirm the exact pattern of allele inheritance. JC (the index child) almost certainly inherited the same paternal allele and maternal alleles as his affected sibling, CC at D15S210, GABRB3 and MS14 and also quite possibly at and IR4. However, GC, also affected, inherited different alleles to his affected siblings at MS14 and D15S210 and possibly also at IR4 and GABRB3.

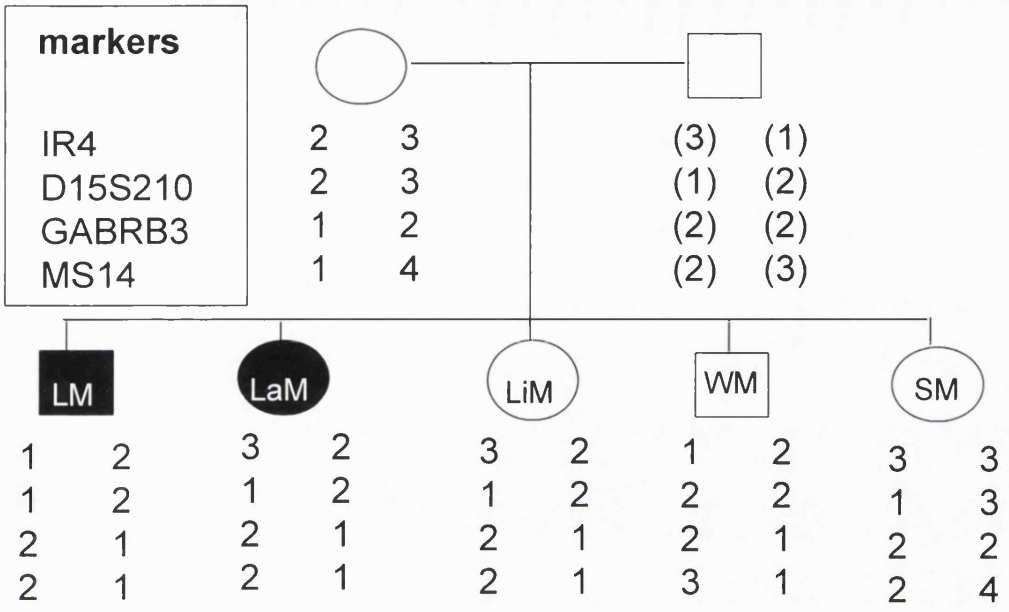
Figure 4.6.2.1: family C: sibling pair linkage analysis



In family M[1], maternal but not paternal DNA was available. DNA was gathered from two affected and three unaffected full siblings. The results are described in figure 4.6.2.2. As paternal DNA was unavailable, those alleles have been inferred on the basis of his children's allele pattern. LM and LaM were both affected, and although they both almost certainly inherited the same maternal and paternal alleles at D15S210, and MS14 and possibly at GABRB3, so did an unaffected sibling (LiM).

[1] Family M are part of a retrospective series, not the current sample

Figure 4.6.2.2: family M: sibling pair linkage analysis



4.6.3 Summary

Methylation status studies and sibling pair linkage testing, almost certainly disprove the coinheritance theory. All HSS affected children tested to date showed a normal methylation pattern at 15q11-13, excluding the anomalies associated with PWS at 15q11-13. At each of the four linkage markers there is not complete coincidence between paternal or maternal alleles at the PWS region for affected siblings. As the markers used are regarded as tightly linked to the PWS region (Mutirangura et al, 1993), it is most unlikely the PWS and HSS locus coinherit.

Chapter 5

5.0 Discussion

5.1 Section A summary and discussion of results

HSS manifests in conditions of stress:

5.1.1 Psychosocial adversity

The stressed group had significantly more frequent social services involvement than the HSS group. However since the stressed group were recruited on the basis of social services involvement, this was not surprising. The PWS group families had been referred significantly less frequently than either of the other groups. The investigation aimed to assess social services involvement due to psychosocial concerns in the family, rather than in relation to services that are provided for children with special needs. Those families in the PWS group who received social services help to organise school transport and so on were not included in the comparison.

Despite being recruited consecutively only on the basis of the HSS diagnostic algorithm, 68% of the HSS group (17 cases) were subsequently found to have social services involvement. Referral of this kind is 4 % in the general population (Skuse and Bentovim, 1994). This suggests that the families in which there is a child affected with HSS are distinct from the general population.

By setting an hypothesis of stress association there is a temptation that one will 'find' stress in an affected child's environment where in fact there is none. There are descriptions in the literature of post hoc and unsystematic judgements about the environments from which affected children came. For example, Hopwood and Becker (1979) described one child's stressful experience as having 'emotionally absent father'. While it is acknowledged that clinical opinion is in some cases the most accurate appraisal of psychosocial adversity, the clinician should be unaware of the diagnosis, in order to validate the theory of psychosocial adversity in association with PSS or HSS.

In the present study, those families found to be involved with social services subsequent to their diagnoses are viewed as having been assessed objectively and independent of potential bias. Although a remaining 7 HSS cases did not have social services involvement (at the time of assessment) various professionals had recorded concerns about each child's psychosocial environment. We would suggest that the clinical appraisal in these remaining cases was more robust than many of those in the literature, for the following reason. In 6 cases assessments were made by professionals unaware of the diagnosis of HSS and its hypothesised stress associations. Of these cases, two head teachers had contacted Great Ormond Street Hospital spontaneously to raise their concerns about a child's family circumstances.

We would acknowledge that the categories of abuse into which children are put on 'at risk' registers, for example, can sometimes be rather arbitrary. The central issue is usually that they are of concern at all. However, bearing these limitations in mind, there was no evidence that the type of abuse (confirmed or suspected) differentiated the HSS and stressed groups. Physical, sexual, emotional and physical abuse occurred at relatively comparable frequencies in both groups. It may be suggested that this result excludes the possibility that HSS is a non-specific reaction to a particular type of stress.

Parents in the HSS and stressed groups reported using frankly abusive reprimands significantly more frequently than the care-givers in the PWS group, despite two potential confounding factors. First *all* parents may minimise their behaviour when they report the type of punishment they metre out to their children. Second, if they are aware their actions are abusive, abusing parents may minimise to a greater degree than non-abusive parents. Certainly some parents appeared unaware that they mistreat their children. One mother commented that she was appalled by parents who lock up their children. She then described locking her daughter in her room overnight, as a punishment, but suggested that her behaviour was acceptable because she only used 'a small lock'. Other parents described biting their child, or destroying a favourite toy in front of the child because they believed it was the only way to stop their child misbehaving.

The evidence from these analyses would support the hypothesis that HSS manifests in conditions of psychosocial adversity and chronic stress.

5.1.2 Expressed Emotion (Vaughn and Leff,1976b)

Each dimension in the Expressed Emotion rating scale was examined individually. Absolute number of critical comments, hostility, emotional over-involvement and the number of positive comments were not significantly different between the groups. These findings did not support the hypotheses, though the data (with the exception of positive comments) demonstrated non-significant trends in the predicted direction. Though these analyses were important in order to explore the data thoroughly, it is not surprising that as continuous variables, some sub-scales did not differentiate the groups. The literature reports that EE ratings have predictive validity only as a dichotomous variable, high or low EE.

The HSS group care-givers were rated as significantly less warm regarding their child, than either the stressed or the PWS group care-givers. This sub-scale indicates a degree of emotional detachment in describing the index children. Note that the HSS group care-givers were less warm towards their children than the *stressed* group care-givers. This lack of warmth raises questions about the quality of attachment the care-giver has to (in most cases) her child, as opposed to the child's attachment to their care-giver. Vostanis et al (1994) also found that maternal warmth was significantly lower towards children with conduct disorder and emotional disturbance than an age, sex and SES matched control group. It may be that the HSS group caregivers' emotional detachment means that they are rather indifferent to their child.

Conversely, the HSS caregivers did not seem indifferent to their child's hyperphagic behaviour. The HSS group was significantly more likely to be hyperphagic than the stressed group and accordingly their care-givers made significantly more food related critical remarks than the stressed group. However for individual case correlations, the frequency of food related critical comments was not significantly related to the reported severity of hyperphagia in the HSS group. In other words as a group, HSS care-givers are highly critical of their child's appetite disturbance, but in individuals, criticism is not directly proportional to the severity of reported behaviour.

There was no significant correlation in any of the three groups between behaviour disturbance and non-food critical comments. It may be worth bearing in mind, that despite the three groups having very similar levels of behavioural disturbance on many dimensions, there was a trend (which just missed significance) for the PWS group families to make fewer critical comments. Vostanis et al (1994) reported that there was a significant relationship between their child behaviour ratings and the number of critical comments in a sample of non-referred comparison children, and children with emotional and behavioural disorders. There is evidence that the number of critical comments, for example, increases in some families when the patient's behaviour or symptoms are worse (Kavanagh, 1992). However the key issue is that the likelihood of care-givers who are high EE is *independent* of the severity of the psychopatholgy in patients with schizophrenia (Vaughn and Leff, 1976b) and depression (Hooley, Orley and Teasdale, 1986). This suggests that the dichotomous rating of high or low EE should be unrelated to the severity of childhood behaviour disturbance.

The most crucial comparison involved the dichotomous rating of high or low EE. High EE is indicative of intra-familial stress . In other words, high EE is an index of stress experienced (Koenigsberg and Handley, 1986) by the children in their family relationships. It is important to note that high EE is not synonymous with abuse. It is a type of relationship described in many different family types. However Vostanis and Nicholls (1992) reported that none of the parents in their study of a non-referred group were high EE. Further low EE caregivers are described, across various cultures, as having greater empathy and understanding, more tolerant, having greater-problem solving skills, less intrusive and confrontational - in sum less 'emotionally arousing' (pp17) than high EE relatives (Vaughn, 1989) . Further Hibbs, Hamburger, Markus, Kruesi and Leanane (1993) noted that high EE was associated with family conflict and parental mental health difficulties. Hibbs, Zahn, Hamurger, Kruesi and Rapoport, (1992) validated the concept of arousal with physiological data. They showed that children living with two high EE parents had higher skin conductance (an index of physiological arousal). In the present study only the principal care-taker was rated for EE but the principle may apply to our sample.

The hypothesis was supported in this case, with both the stressed and HSS groups being significantly more likely to show high Expressed Emotion in comparison to the

PWS group. This suggests that the HSS and stressed groups are living in comparable degree of intra-familial stress. It is important to note that our EE ratings were not made in a time of crisis for the families (as is the case in some EE studies) but in the usual family circumstances. This might increase the likelihood that the emotional style expressed at interview was representative of the experience the child has from day to day.

There is some suggestion that living with high EE relatives may have a causal link as opposed to an association, with psychiatric patient relapse (Vaughn, 1989), which may lead to speculation that EE may have a contributory effect on the *onset* of some psychiatric conditions in those individuals who are vulnerable. Such a line of debate sits well with the theoretical basis of HSS. Though it certainly cannot be the only factor in the onset of the condition, as some families in the HSS group were not high EE and many frankly abusive families may not be rated as high EE. Much of the EE literature describes adult offspring and their relationship with parents (and in some cases, siblings or spouses). These relationships are crucial to a vulnerable adult's mental well-being (eg Vaughn, 1989). The quality of relationship that a *child* ,as opposed to an adult, has with their main care-giver, (who is probably their main attachment figure), might be viewed as even more intrinsic to psychosocial health.

5.1.3 Family Environment Scale (Moos and Moos,1986)

There are 10 sub-scales in the FES, each describing a different aspect of the family environment. As predicted, the stressed group were significantly lower on cohesion and expressiveness sub-scales and higher on conflict and control sub-scales in comparison to the PWS families. This profile of less cohesion and expressiveness in abusing families than SES matched controls is described by Perry, Wells and Doran (1983). The HSS families, against the hypotheses, were not significantly different from the PWS group on these sub-scales. However, at the same time they were not significantly different from the stressed group either. The PWS and stressed groups reported themselves as being on each end of the dimension, with the HSS families mean score being between the other two groups.

As with the expressed emotion scales, perhaps the most interesting results were the groups' family type categories. Both the HSS and stressed groups were classified as 'disorganised', while the PWS group narrowly missed the 'support orientated

classification'. A disorganised family is associated with the risk of abuse or neglect (eg Long and Jackson,1994). This would support the hypothesis that the HSS affected children are living in conditions strongly associated with stress. That the HSS group families are of a similar type to the stressed group, who are by definition living in stressful circumstances, would add further weight to this argument. Groups were analysed to examine the proportion of individual families in each category. The stressed group was significantly less likely to be support orientated than either the HSS or PWS group. Once again the trend was for the stressed and PWS groups to be at the extreme of the distribution, with HSS at the mid point. In this case, however the stressed group was significantly different from the HSS group, in lacking support orientation.

Although it may be argued that on the single sub-scales scores, the evidence does not support the stress hypothesis, it does not disprove it either. Vostanis et al (1994) suggest that EE may be a more objective measure of family circumstances than the self reported Family Environment Scale. The categorisation of disorganisation associated with psychosocial adversity provides evidence that both the stressed and the HSS groups' families have comparable family circumstances which are distinct from the families in the PWS group.

5.4 Physiological stress reactivity (salivary cortisol)

There were no significant differences between the groups in baseline salivary cortisol levels, but as there was such wide intra-individual differences in children and adolescents' cortisol levels (Bauer et al, 1993, Kiess et al, 1995), this result was expected to some extent. The human system habituates in chronic stress, so that cortisol levels, though elevated initially in stress, return to within normal limits (Hellhammer and Wade,1993 , Scaubroeck and Ganster,1993 for example). This is also documented in the animal literature (Kant, Bauman, Anderson and Moougey,1992). There are also studies, describing contradictory results, showing significantly elevated levels of cortisol in chronically stressed humans (Davidson, Weiss, O'Keffe and Baum, 1990) and some argue that there is a lack of convincing evidence concerning the effects of chronic stress on salivary cortisol in humans (Kirschbaum and Hellhammer, 1989).

Baseline cortisol levels in the normal comparison group were relatively similar to a normative sample described by Kiess et al (1995). They noted that for children aged 5 to 8 years and 8 to 18 years, at 1pm salivary cortisol was 4.9 (sd 4.2) and 5.0 (sd 6.2) units respectively as compared to the 6.69 (sd 4.16) units for the normal comparison children in the present study. Laboratory procedures can systematically alter readings, making cross lab comparison difficult (Kirschbaum and Hellhammer, 1989).

Though cortisol may be positively correlated with obesity (Kiess et al, 1995), we found no significant relationship between obesity and cortisol across the full sample or within each group. However our results fit with those of Tu, Hartridge and Izawa (1992) who described normal cortisol levels in three 15 year old boys with PWS, who were obese.

The key hypothesis was that the stressed and HSS group children would show a characteristic HPA recovery following an acute exercise stressor. All groups were stressed to an equivalent degree by the exercise, as measured by their pre-test and post-test pulse rates. There were no group specific HPA recovery profiles, a result which failed to support the hypothesis. In other words, HSS, stressed, PWS and the normal comparison group all demonstrated comparable HPA profiles following the acute stressor. In contrast, Hart, Gunnar and Cicchetti (1995) suggested that a sample of young maltreated children showed a blunted HPA response in comparison to an SES balanced comparison group. Like the present study, they found no differences in baseline cortisol levels. There are some methodological concerns in this study as they used social conflict as the acute stressor, measured by observational and teacher ratings. Hart et al (1995) note that the case and comparison children were in different schools so the degree of social conflict may be systematically different across groups nor was there any rating of acute stressors at the children's home. The acute stressor may not have been constant across the groups. The advantage of an acute physical stressor, is that children have exposure to the same degree and quality of stressor.

The negative finding in the present study may be due to the level of stress that the children experienced during the exercise. Kirschbaum and Hellhammer (1989) describe a pilot study in which salivary cortisol responses increased in men by a

factor of 2.5 after a 5KM run. Further they note that as the severity of the stressor increases, the cortisol response increases proportionately. In the present study the changes in cortisol level (from baseline to peak response) were 10.5%, 53.5%, 11.0% and 12.2% for the HSS, PWS, stressed and comparison groups respectively. Kirschbaum and Hellhammer (1989) noted that cortisol levels in the saliva should peak 20-30 minutes following the acute stressor. Our data certainly show that trend (during a time period when cortisol levels are falling according to circadian rhythm) but the increase was not significant. This indicates that the stressor was having an effect but not to a significant degree. The children in this study were 'stressed' following the exercise but certainly not in distress. It may be that a more challenging stressor would have produced the predicted results. However, the ethics of significantly elevating the degree of stress without a direct secondary gain are questionable. Taking blood might be an appropriate acute stressor, but only if a blood sample is required for other purposes.

The physiological assessment of stress reactivity within the groups failed to support the hypothesis, but neither did the results disprove the theory that HSS is a stress reactive syndrome.

5.2 Section B summary and discussion of results

HSS phenotype definition and comparison with PWS

5.2.1 Definition of a Phenotype:

The analyses described below attempts to clarify two issues. First we examine the degree to which HSS and PWS exhibit similar behavioural, cognitive and physical profiles. By demonstrating that HSS and PWS are phenotypically identical does not necessarily imply that HSS is a genetic phenomena. It may be that HSS is a phenocopy of PWS - the same clinical picture resulting solely from environmental factors, rather than being genetically determined. (Friedman, Dill, Hayden and McGillivary 1992). Alternatively as Flint and Yule (1994) note the same phenotype may result from two distinct genotypes.

Second, in an attempt to identify which features of HSS are 'the phenotype' and which might be attributed to a normative stress response, the HSS children were compared with the stressed group. By definition all cases of HSS were hyperphagic (and of short stature). If there is proof of a genetic basis and evidence that hyperphagia is not characteristic in the stressed group, hyperphagia might constitute the part of the 'HSS phenotype'. Flint (1996) notes:

'A behavioural phenotype can be defined as a behaviour...consistently associated with, and specific to a syndrome with... a genetic aetiology' (pp355).

Flint suggests that in cases where affected individuals demonstrate a behaviour more often than an appropriate comparison group, but it is not invariably present, such behaviour should be termed 'syndrome specific' rather than part of a behavioural phenotype. In syndrome specific behaviour there may be some doubt about the whether the lesion directly or indirectly causes the characteristic behaviour. Using this definition, if children affected with HSS demonstrate a feature more frequently than the stressed group but not invariably, then that feature may be syndrome specific.

Einfeld and Hall (1992) set out the minimum criteria in defining a behavioural phenotype:

1. Evidence of association using case-control studies
2. Type I errors should be avoided
3. Confounding variables such as age sex and IQ should be held constant.
4. Standardised measures should be employed where possible.

Einfeld and Hall's third point is fundamental. In their review of the literature, Flint and Yule (1994) note the importance of taking cognitive ability into account in describing phenotypes. In the present study we have balanced the groups for age, sex, SES (and where appropriate, stress) so the effects of these factors are negated. By covarying IQ in the analyses, the effect of cognitive disability is also controlled.

5.2.2 Cognitive ability

5.2.2.1 HSS in comparison to PWS

The PWS group had significantly lower full scale, verbal and performance IQ scores in comparison to the HSS group. This result did not support the hypothesis of similar cognitive ability between the HSS and PWS groups in global ability. Full scale IQ in the present study's PWS group (mean score 54) was only slightly lower than previous reports of mean scores of around 62 (eg Dykens, Hodapp, Walsh and Nash, 1992b). This suggests that the present PWS sample is fairly representative of PWS in their cognitive ability.

It is possible that HSS affected children may have comparable strengths and weaknesses within their cognitive profile to children with PWS, despite functioning at a higher level. Various cognitive styles have been associated with PWS, though a lack of appropriate comparison groups in many studies means that it is not clear whether these profiles are specific to the syndrome. For example, children affected with PWS are reported to have relatively good puzzle solving (or visuo-spatial) ability (Holm et al,1993). The present study's results do not indicate particular visuo-spatial strengths in PWS affected children as measured by the block-design sub-scale in the WISC (Wechsler,1992). The PWS group block design standardised score was 2.9 as compared to 2.7 in the picture completion (another performance task) and 3.7 in similarities and 2.6 in vocabulary (both verbal sub-scales). A similarly low block design score, in a series of children with PWS, was described by Gabel et al (1986) who reported the block design standard score ranking number three in four sub-scale scores of the WISC-R (Wechsler, 1974). This result may be because block-design does not capture the PWS group's visuo-spatial abilities adequately.

A second cognitive style associated with PWS is that attainment is superior to mental processing or performance IQ (Dykens et al 1992b). This rather contradicts the theory that individuals with PWS have relatively superior visuo-spatial abilities, as these same visuo-spatial abilities are part of performance IQ. Our data support, in part, the theory of attainment superiority, if we assume that verbal IQ is an accurate index of attainment as suggested by Yule, Gold and Busch (1981 and Kline,1991). 73% of the children in the PWS group had a comparatively even profile across verbal and performance IQ, but of those with a significant discrepancy, 75% had a significantly higher verbal IQ. The results, do not endorse the findings of Curfs et al (1991) who suggested that performance IQ was relatively stronger than verbal IQ in

individuals with PWS, but fit with Sulzbacher's (1988) suggestion, that children with PWS are interested in reading - and therefore vocabulary tasks.

Do the children with HSS show similar cognitive qualities to the PWS group, but at a higher cognitive level? Without administering a more extensive battery of neuropsychological tests, it is not possible to test this thoroughly. The data available indicate that the nature of abilities, in addition to the level of ability, is distinct between the HSS and PWS groups for two reasons. First, significantly more children with HSS had a verbal versus performance IQ discrepancy, in comparison to the PWS group. Second, of those children who did have a discrepancy only 22% of HSS affected children showed superior verbal skills as compared with 75% of the PWS group.

IQ stays at a fairly constant level across age groups in PWS according to Dykens's et al (1992b) who examined IQ stability, both longitudinally and in a cross-sectional design with a population aged 5 - 46. Other studies have suggested IQ declines with age on the basis of cross-sectional data (Crnic, Sulzbacher, Snow and Holm, 1980). Neither the PWS or HSS group showed any significant IQ change across the age range described in the present study. This is not particularly supportive of characteristic cognitive similarity between HSS and PWS, as it is more likely that there would be stability in cognitive ability as opposed to significant age related changes.

5.2.2.2 HSS in comparison to the stressed group

The evidence for cognitive ability equivalence between the HSS and stressed group is stronger. There were no significant differences between full scale, verbal and performance IQ when HSS and stressed groups were compared. Further 50% of stressed and 60% of HSS children showed a verbal versus performance IQ discrepancy. Of the children with significantly different scores, 78% of HSS and 58% of the stressed children scored significantly higher on performance IQ. This pattern of performance IQ , being higher than verbal IQ in many of the HSS and stressed children fits well with the literature describing the cognitive profiles of abused or neglected children (eg Walsh,1990). Wechsler (1992) also notes than such a discrepancy is often described in children with emotional and behavioural problems, which may include children in adversity.

Other studies report that abused children's overall cognitive ability is depressed in comparison to the general population (Perry, Doran and Wells 1983, Eckenrode, Laird and Doris,1993) but Rutter (1985c) cautions that many of the significant differences may be an artefact of socio-economic status (SES). In the present study, full scale IQ scores of 78 and 84 for the HSS and stressed group respectively put both the groups in the 'low' and 'low average' ability ranges respectively, according to the WISC classification (Wechsler, 1992). However, without SES matched non-stressed comparisons, it is impossible to suggest why their scores should be so low. It may be due to socio-economic status or it may be a non-specific stress response. There is a third possible explanation in the HSS group. It may be that cognitive disability is part of the HSS syndrome. Data comparing affected with unaffected siblings, in which family circumstances are held constant, suggest that this is the case (discussed further below). Further, the mean IQ score of 78 is almost identical to the group mean of 76 recorded in Skuse et al's (1996) series of HSS affected children. IQ scores in this range may be a characteristic aspect of the syndrome. However, the comparison between the index children in the HSS and stressed groups cannot make that differentiation.

5.2.2.3 Summary

The cognitive profile of the HSS and PWS groups are quantitatively and qualitatively distinct. Conversely there are broad similarities between the HSS group and the stressed children's IQ score patterns. The aetiology of the cognitive deficits remains unresolved.

5.2.3 Anthropometric data

5.2.3.1 HSS in comparison to PWS

Children with HSS were significantly shorter than those with PWS. Although PWS is most commonly associated with short stature, there are also reports of children affected with PWS who are of normal stature, or even tall stature, on the 90th centile (Harty et al 1993). This occasional finding was evident in our sample as one girl with PWS was 1.76 sds above the mean in height. It is clear that the PWS group certainly tended to be short for their age at -1.5 sds below the population mean, and were

significantly shorter than the stressed group. Ritzen, Per Bolme and Hall (1992) described a series of children with PWS under 10, with a mean height of -1.4 sds, almost identical to the present study. They note that individuals with PWS may become proportionately shorter with age, as their adult sample were -3.8 sds in height.

There is some evidence that children with PWS are short secondary to GH insufficiency, even in comparison to obese individuals (Ritzen, Per Bolme and Hall, 1992). There is similar evidence in children with HSS (eg Powell et al, 1967b and Skuse et al, 1996). However children with PWS respond well to GH therapy (Angulo, Castro-Magana, Uy and Rosenfeld, 1992,), but the literature describes children with HSS responding relatively poorly to GH therapy (Frasier and Rallison, 1972, Tanner, 1973). Both the HSS and PWS group are characteristically short in comparison to the normal population, but it is not clear, partly because obesity confounds many PWS studies, if the aetiology of short stature in the each group is similar.

The PWS group had a significantly higher Body Mass Index (BMI) than the HSS group. Ritzen et al (1992) report a BMI presented as a non-standardised figure of 25.7 which is approximately 3.15 sds above the mean, and therefore higher than our PWS group mean of 2.40 sds. It may be that some of the increased body weight is due to the fact that Ritzen et al's (1992) sample of PWS affected individuals was older than the presented study, ranging up to 19 years. Adolescents and adults with PWS may have more access to food because they are relatively independent. This is discussed further below. Butler (1990) notes that there is debate in the literature about the contribution that calories consumed, activity level and basal metabolic rate may have in contributing to obesity in PWS. Using objective measures, Davies, Joughhin, Livingstone and Barnes (1992) demonstrated that obesity in the PWS children may be exacerbated by a significantly lower total energy expenditure than normal children (after controlling for body composition, sex and age) There was no evidence that obesity in PWS may be exacerbated by a low basal metabolic rate. No comparable studies have been done with children with HSS. Such information would be invaluable, and may illustrate why the HSS group children have a BMI almost at the population mean, despite being hyperphagic. Possible explanations may be that the HSS affected children have a metabolic abnormality or that parents prevent excessive food intake or perhaps a combination of both.

5.2.3.2 HSS in comparison to the stressed group.

The HSS children were significantly shorter than the stressed children, but not significantly different in terms of BMI. Much of the literature concerning growth and abuse or stress is confounded by malnutrition or economic deprivation. The stressed and HSS children were in groups balanced for SES and so this factor did not contribute to the difference. Karp, Scholl, Decker and Ebert (1989) examined an abused population relative to an SES matched comparison group. Abused children were significantly more likely to show wasting than comparisons but there was no evidence of short stature or stunting in the abused group. Our study replicates this finding in the stressed group, though it is worth noting that the standardised height mean of the stressed group was slightly below the general population mean.

5.2.3.3 Summary

The data from the present study would support the theory that stress is not generally associated with significantly short stature. A consecutive series of children in stressed circumstances (our stressed group), did not show significant growth retardation. Given data provided by Taitz and King (1988) we might suggest that there are some stressed children who do not have HSS but show poor growth velocity. As discussed in 1.3.3, it may be that anorexia is the most likely explanation in these cases. Our evidence suggests that severe growth retardation with a normal BMI is a specific stress response associated with the syndrome of HSS, rather than a normative reaction.

5.2.4 Child Health History

5.2.4.1 HSS in comparison to PWS

Children with PWS were reported to have hypotonia and weight gain problems more frequently or to a greater extent than children affected with HSS. A logistic regression showed that reported hypotonia identified by medical professionals discriminated between the groups to a greater degree than failure to thrive. The children in the PWS group were also significantly more likely than children with HSS to have neonatal health problems and show delayed motor milestones.

No significant differences were found between the PWS and HSS groups in birth-weight, taking into account ordinal position, maternal height, and the frequency of maternal smoking or drinking during the pregnancy. Nor were there significant group differences in gestation age or in the maternal proportion of pregnancies surviving birth.

Butler (1990), in a review of 538 individuals with PWS found 94% were hypotonic (compared to 93% in the present study) and 93% had feeding problems (97% in the present study, of whom 87% were labelled as failure to thrive). Only 30% of PWS cases in Butler's review had a birth weight below 80 ounces (compared to 33% in the present study). These data would indicate that the present sample of PWS is representative of PWS in terms of child and neonatal health.

The results indicate that HSS and PWS are distinct on the basis of motor milestones and neonatal health. In weight gain and hypotonia the PWS group show more problems than the HSS group, but importantly, children with HSS were *also* significantly more likely to demonstrate these problems than the stressed group (discussed below). The PWS and HSS were comparable on a number of other neonatal health variables but as the factors were not significantly different in the stressed group either, this does not indicate these features are characteristic of either syndrome.

5.2.4.2 HSS in comparison to the stressed group

The HSS group were significantly more likely to show weight gain problems and hypotonia than the stressed group. Further exploration of this factor showed that the HSS group were significantly more likely than the stressed children to be labelled as failure to thrive. That these factors differentiate the groups suggests an *organic* difference between them (though failure to thrive is certainly not invariably an organic condition). Organic differences between the HSS and stressed group would support the theory that children with HSS are physiologically distinct from the stressed group, as illustrated by their physiologically distinct reaction to stress - the HSS syndrome.

The HSS and stressed groups, conversely, had comparable profiles in neonatal health, milestones, gestational age and proportion of maternal pregnancies surviving birth. In addition, the groups had similar birthweights when ordinal position,

maternal height and the likelihood of maternal smoking or drinking during the pregnancy were taken into account.

Sherrod, O' Connor, Vietze and Altemeier (1984) examined the correlates of abuse and neglect on infant and child health. They found no significant differences in birthweight or gestational age between comparison children, those who had been neglected or abused, or had non-organic failure to thrive. Nor was there any significant difference in terms of apgar scores which might predict developmental milestones. This suggests that one might expect to find comparable child and neonatal health profiles between HSS, stressed and the normal population. These variables seem to be neither characteristic of the stressed population as a whole nor of HSS.

5.2.4.3 Summary

The HSS group was not convincingly similar to the PWS group in infant health. Comparisons between the HSS and the stressed children suggest that weight gain problems and hypotonia may be a characteristic marker of HSS. Given that hypotonia (and possibly the potential to fail to thrive) are present at birth, it is conceivable that these markers *pre-date* the manifestation of HSS, irrespective of the environment to be encountered by the child. These findings require validation using medical records and physical examination, rather than parental report.

5.2.5 Hyperphagia and appetite disturbance

5.2.5.1 HSS in comparison to PWS

There was no significant difference in the degree of reported general hyperphagia in the HSS and PWS groups. This is crucial if we are to suggest that children with HSS are hyperphagic, rather than that they have a particularly healthy appetite. Hyperphagia should describe appetite disturbance, not just an appetite at the extreme end of the normal distribution. It is an important validation of HSS that it is indistinguishable from the 'gold standard' hyperphagic condition.

There was some evidence to suggest that the children with HSS have a more severely disturbed appetite than the PWS group. For hyperphagia at school, 'other hyperphagia' and polydipsia, only the children with HSS showed significantly more hyperphagic features than the stressed children. This indicates that though the HSS

and PWS groups were not distinct, neither were the PWS groups significantly different from the stressed groups. It is important to remember that these three variables were constructed from summed variables. 'Other hyperphagia' included the variable gorging *and vomiting*, and pica/polydipsia contained a measure of polydipsia. Both these specific variables may be significant to PWS and are further described below.

That the HSS group but not the PWS group were reported by teachers to be significantly more hyperphagic than the stressed group, might be explained by the type of schools the children attended. 28% of HSS affected children as compared to 63% of the PWS group attended a special needs school, where staff are likely to be educated about PWS and the importance of weight control. PWS group care-givers often commented that their child's school was extremely vigilant concerning food, in order to prevent opportunities to steal food and so on. The schools in the HSS group also took precautions but *in response* to hyperphagia, such as locking school lunches away. There may be more opportunities to demonstrate hyperphagia in a mainstream school than in a special needs school which is informed about PWS.

There was no evidence of age related trends in either the HSS or the PWS groups' hyperphagia according to parents and teachers (though the HSS group were significantly less likely to show pica/polydipsia with age). Longitudinal data would be more informative, but these results do not suggest that hyperphagia increases (or decreases) with age. The literature reports that hyperphagia usually starts in PWS before the age of six years (Holm et al, 1993). Curfs (1992) suggests that the hyperphagic behaviour becomes increasingly marked with age but there are no data or reference to support this claim. The children in our PWS sample were aged five to fifteen years old. It seems that their behaviour, which may be distinct from their craving, is relatively constant across our study's age range. During middle childhood, the amount eaten by children with PWS may be relatively easy to control. It is usual to have meals prepared, and snacks monitored by parents, for any child. Further, with increasingly early diagnosis, families implement an appropriate diet before hyperphagia manifests as they are pre-warned about the problems. It may be that the new generation of PWS affected individuals and their families are educated to prevent obesity in the first place and to maintain a constant diet, at least during childhood. Problems may arise during adulthood when independence is encouraged

and the individual may have to develop a greater degree of self-discipline around food.

By examining figure 4.4.6.1, it is clear that the quality of appetite disturbance is very similar between the HSS and PWS groups. Each type of behaviour described in children with PWS is also described, often to a greater degree in the children with HSS. Item by item analysis showed that the HSS group was significantly more likely to gorge *and vomit* than the HSS group. Individuals with PWS very rarely vomit (eg Holm et al, 1993) and this may be due to the poor muscle tone associated with PWS. There are no such reports in the HSS. Note also that there is no significant group difference in the 'over-eating requiring restraint' variable which suggests that the propensity to vomit rather than to over-eat is significantly different between HSS and PWS.

Polydipsia was described in the HSS group more frequently than in the PWS group. In fact many PWS group parents commented spontaneously that they would prefer their child to drink *more.* They suggested that unless there were drinks available that their child liked, such as milk-shakes, their children would not ask for a drink. Robinson et al (1992), in support of this observation, reported that parents in their study reported PWS affected children avoided drinking water. The care-givers of the children with HSS, in contrast, described children who seemed desperately thirsty. The HSS affected children commonly drank water, suggesting they were not particularly interested in taste. Parents reported that, after their child had drunk what they considered a reasonable amount, they would refuse further drinks. This refusal was often because care-takers reported their child's excessive drinking led to deliberate urination around the house or wetting the bed at night. If HSS affected children were refused drinks by their care-giver, some were reported to drink rather unsavoury liquids. One affected boy drank from the toilet habitually and continued to do so, despite his mother putting blue bleach in the toilet water to deter him. We watched another boy 'drink' a cup of cold tea belonging to his mother. He 'poured' the tea into his mouth, barely taking a breath. This incident happened during an in-patient hospital stay , when one would assume that adequate liquid was provided. The children with HSS seem to have an excessive thirst, a feature also evident in the series described by Skuse et al (1996), while the children in the PWS group seem to drink quantities more comparable to the stressed group.

Though Flint (1996) suggests that the diagnosis of PWS might be questioned if a child did not over-eat, the children in the present sample of PWS demonstrated wide variability in their phenotype. For example one boy, with a classic deletion at 15q11-13, aged 7 years, occasionally took food from the kitchen. His mother reported that this was becoming less frequent as time went on. He was short for his age (with his height at 1.04 sds below the mean) and certainly not obese (BMI = -0.45 sds below the mean). It is possible that he will become hyperphagic as he grows older, but at the time of assessment he would not be identified as hyperphagic according to the HSS diagnostic algorithm. Without a genetic marker for HSS, behaviour must dictate caseness. It is possible that there may be the same degree of variability in the HSS syndrome as there is PWS.

5.2.5.2 HSS in comparison to the stressed group

The HSS group showed more severe behaviour than the stressed group on all four aspects of appetite disturbance: general hyperphagia, hyperphagia at school, 'other hyperphagia' and pica/polydipsia. The item by item analysis showed each item (except chewing non-food) differentiated the groups, with the HSS group showing significantly more appetite disturbance than the stressed group. There is a lack of literature on pica but Bicknell (1975) noted that children who show pica live in environmental and psychosocial adversity and/or in whom there is developmental delay, though she noted that in the general population, pica is rare. Benoit (1993) also suggested that pica can be, in some cases, associated with child maltreatment, poverty and other psychosocial pressures. Our data suggest that stressed children were significantly less likely to show pica than the HSS group, indicating that it may not be a common childhood feature even in a stressed population.

It is notable that none of the stressed children, according to parents, had gorged and vomited, or stolen food from school, while 48% had gorged and vomited, and 52% had stolen food from school in the HSS group.

One stressed child (and his full sister, described further in 5.3.2.3) fitted the HSS diagnostic algorithm only in terms of hyperphagia. He perpetually stole food from home early in the morning or at night, hoarded food, ate excessively requiring restraint but he didn't gorge and vomit, show pica or polydipsia, or steal from school

according to his mother (though he did according to his teacher). He did not fit the HSS algorithm in terms of his height as he was on the 75th centile. Interestingly, he was rather thin, with a BMI of -1.65 sds below the mean. One might speculate and suggest that this boy has a variation of HSS in the context of stress, but his height is unaffected. Perhaps he has a metabolic disorder which means that he eats excessively but does not gain weight. We might hypothesise that HSS affected children have a BMI around the population mean *only* because they are short and therefore need fewer calories than if they were taller. In other words, if this boy had been short, his BMI would have been closer to the population mean. Alternatively, he may be a true case of HSS but his retarded growth velocity has not yet resulted in short stature. However, according to his mother, he had been hyperphagic since he was approximately six years old, which, we might speculate means he has been 'affected' since that age. Without longitudinal records it is not possible to record his height velocity.

5.2.5.3 IQ and hyperphagia

It was important to covary IQ in all these analyses. Some studies have suggested that hyperphagia or obesity is a consequence of low IQ, reporting excessive appetites in individuals with Downs syndrome, for example (Bell and Bhate, 1992). However Holland et al (1995) note that the problem is less severe in these cases in comparison to PWS, and conclude that the learning difficulty per se is not the cause of hyperphagia. Previous studies (Crnic, Sulzbacher, Snow, and Holm, 1980) claiming IQ in PWS was associated with weight (and by implication, the degree of hyperphagia) were flawed because height was not taken into account. Further, the Crnic et al (1980) study implied a rather counter-intuitive causal link between weight and IQ on the basis of correlational data. They suggested that weight control might prevent IQ decline. Dykens, Hodapp, Walsh and Nash (1992) found no such relationship in their study of IQ and its relationship with BMI which does take height into account. Our results support Dykens et al (1992). Within each group in the present study there was no significant relationship between any of the aspects of reported hyperphagia and IQ or between IQ and BMI.

5.2.5.4 Summary

As a group, it is clear that stressed children are neither hyperphagic nor polydipsic, a result that strongly supports the hypothesis that hyperphagia is a specific stress

response inherent to HSS. Further evidence from the comparison between the HSS and PWS groups suggested that the quality and degree of appetite disturbance, according to parents, is in most cases indistinguishable.

5.2.6 Self reported and observed psychosocial adjustment (CAS, Hodges,1978)

5.2.6.1 PWS in comparison to HSS

There were no significant differences (using the corrected alpha) between the PWS and HSS groups. This might suggest that the two syndromes have parallel psychosocial profiles but, as there were no significant differences in comparison to the stressed children either, it is more probable that there are no characteristic patterns of psychopathology in either group, according to the children themselves. The observational items in the CAS also failed to reveal any significant difference between the PWS, HSS and stressed groups.

The profiles would be more easily interpreted with IQ matched unaffected comparison groups. Normative data would provide information about the degree of disturbance relative to the general population, rather than relative to each of the groups. Hodges, Kline, Stern, Cytryn and McKnew (1982) report the self reported items mean for a non-referred group, a behaviourally disturbed out-patient group and a behaviourally disturbed in-patient group. Scores[1] were 15.5, 28.9 and 43, for the groups respectively. They report that the each group's score was significantly different from one another, with the in-patients having the higher score and therefore greatest self reported disturbance and the comparisons group having the lowest score. In the present study, the children's scores are similar to the behaviourally disturbed out-patient group. Scores were 32.50 and 25.77 for the HSS and PWS groups respectively. This would indicate, as expected, that both the HSS and PWS

[1] in the present study we did not administer the thought disorder symptomology section - this is taken into account in the Hodges et al (1982) total mean score.

groups in the present study, though not significantly different from one another, are more disturbed than children in the general population.

There was no evidence of age related changes in adjustment in the PWS group on any CAS dimension. The children in the HSS group, in contrast, were more likely to act out and show conduct disorder socialised (aggressive and non-aggressive) with increasing age.

The present study seems to be unique in asking the children with PWS, as opposed to parents or teachers, about their adjustment and therefore it is difficult to relate the results to existing literature. Self report is an important aspect of psychosocial adjustment assessment. Hodges, Gordon and Lennon (1989) argue that particularly when assessing internalising disorders, it is more valid to ask children themselves rather than their care-givers. Nor does there seem to be any documented observational data on psychosocial adjustment in existing studies with which to make a comparison.

5.2.6.2 HSS in comparison to the stressed group

There were no significant differences between the HSS and stressed groups on any aspect of self reported adjustment. Because the stressed and HSS affected children were not distinct from the PWS group either, it might be unwise to suggest that the pattern demonstrated by HSS and stressed children was associated with adversity without an appropriate comparison group. However by comparing the self report items scores reported in Hodges et al (1982) as described above, it is clear that both the groups are rather more disturbed than children in the general population. Mean scores were 32.50 and 31.38 for the HSS and stressed group respectively as compared to scores of 15.5 in a non-referred population and 28.9 in an out-patient population of children with behavioural disturbance.

It is notable that there was no difference between the stressed and HSS group in terms of self-reported symptoms of mood disturbance. Depressive symptoms do not seem to be characteristic of our group of children with HSS as compared to the stressed group. Our findings do not support those of Ferholt et al (1985) who suggested that all of their sample of 10 children (7 of whom were hyperphagic) met DSMIII criteria, though as discussed in 1.3.6.9 this diagnosis is rather dubious. Puig-

Antich et al (1984a,b,c & d) suggested a link between poor GH provocation test response (as opposed to levels recorded over-night) and childhood depression. Our results support the theory that depression does not lead to growth failure in HSS. It seems that the poor GH response reported in HSS affected children is unlikely to be due to disturbed mood because the stressed children showed similar symptom frequencies.

The HSS and stressed groups both showed increasing symptomology with age in acting out, and conduct disorder (socialised, aggressive and non-aggressive). In addition the stressed group showed there was an increase in conduct disorder (undersocialised non-aggressive) and 'other disorder' features in older children. Such corresponding age related profiles in the HSS and stressed groups, in contrast to the PWS group, may be indicative of general age related changes in reaction to stress or it may be an artefact of the age related changes in behaviour observed in the general population. For example Rutter et al (1976) noted that there was a slight increase in the frequency of emotional and behaviour problems in adolescence, as compared to middle childhood, and specifically an increase in school refusal (as well as depression) during adolescence. The CAS acting out scale includes school refusal.

There seems to be a disproportionate amount of literature using care-giver reports of stressed children's adjustment rather than direct assessment of the children themselves. One study that did use direct assessment showed that fear and anxiety features are observed more frequently in abused than non-abused children (Kolko, Moser, Weldy 1988). Other studies using self reports have employed psychiatric non-abused comparison groups (for example Livingston 1987) which are not useful in identifying possible psychopathological responses to general stress. Interestingly Beitchman, Zucker, Hood, Dacosta and Akman (1991), in their review of the literature suggested that while parent and teacher reports consistently illustrate greater adjustment difficulties in abused (or stressed) children as compared to non-abused, there are fewer adjustment differences between the same populations in self reported data. Perhaps children minimise or are not aware of their adjustment problems. Alternatively adults, if they are aware of the abuse, may maximise any difficulties observed in children as they expect there to be negative consequences of abuse. Our study indicates that the children do in fact describe themselves as

relatively disturbed. This might be due to the non-threatening questions in the CAS. The questions are phrased so there is no implication that child is disturbed.

5.2.6.3 Summary

The hypothesis concerns the pattern of self reported and observed psychopathology in each group in relation to the two other groups. The results show that all three groups are indistinguishable from one another but seem to be, as one might predict, more disturbed according to their own report than a non-referred population.

5.2.7 Behavioural disturbance (care-giver and teacher report)

5.2.7.1 HSS in comparison to PWS

Six summary variables using a combination of parent and teacher report were examined. No group, sex or interaction effects were significant for externalising behaviour at school or general externalising behaviour. In other words, parents and teachers reported that HSS and PWS children showed comparable profiles. However, since the stressed children showed a similar pattern too, we cannot conclude that such a profile is characteristic of either syndrome.

The summary variables describing attention problems and overactivity did not differentiate between the groups, according to *both* parents and teachers. We looked at each of the contributing variables separately, as it was possible that the attention variables in the PWS group, for example made a disproportionate contribution to the summed score. However the non-significant group differences were maintained when impulsivity, attention problems and overactivity (parent report) and overactivity (teacher report) were examined individually. There is debate in the literature about activity levels in PWS. For example Nardella, Sulzbacher and Worthington-Roberts (1993) using tachometers and pedometers at a summer camp, suggested there was no significant difference in the range, as opposed to the mean (which they do not report) activity levels of children with PWS and non-obese comparisons. The fact that the children were at summer camp, and encouraged to take part in activities may mean that the data are not representative. An important finding was that for the first week of the camp, there was a significant correlation between activity level and weight loss, indicating that underactivity contributes to obesity in PWS.

Davies et al (1992) used doubly labelled isotopes, measured over a period of 10-14 days in PWS affected children's home environment. Basal metabolic rate was not significantly different from non-obese controls, but the activity levels in the PWS group were significantly lower than comparisons, as measured by total energy expended. Davies et al's (1992) data are derived from objective measures, making their findings more valid than parent or teacher report. However the BMI of Davies et al's group was approximately 4.95 sds, as compared to 2.40 sds in the present study. It may be that our sample were actually more active than the group in the Davies et al study and consequently less obese. There may, of course, be other explanatory factors or systematic differences.

Enuresis/encopresis

There were no significant group effects in terms of encopresis/enuresis at school, between any of the three groups. As before the HSS and PWS groups, though similar to each other were also indistinct from the stressed group. PWS and HSS groups were, in contrast, significantly more likely than the stressed group to show encopresis and enuresis at home. Why should there be a difference in behaviour between home and school? It could be argued that both the PWS and HSS groups soil and urinate significantly more often than the stressed group at school too, but they are not discovered as frequently at school as they might be at home. When a child was reported not to soil or urinate at school , the minimum score was 3. The maximum score was 12. The mean scores in table 4.4.9.1 indicate that teachers describe such behaviour happening in school relatively rarely.

Though the PWS and HSS groups were distinct from the stressed group in terms of their soiling and urination at home, closer examination of the variables showed that there seemed to be different explanations in each group for the same behaviour. Of those children who did show enuresis or encopresis, significantly more parents in the HSS group than in the PWS group suggested that the behaviour was deliberate, to cause impact. Children's behaviour was coded by the interviewer as deliberate only when there was little interpretation required, when care-givers reported urination over belongings or in kitchen receptacles for example. In contrast, when children wet the bed at night, for example, though care-givers might have suggested that this behaviour was deliberate, it was not rated as intentional behaviour. In addition only the PWS group were increasingly less likely to show enuresis and encopresis with

age. There was no such age related change in the HSS group. This finding could be interpreted as being a result of muscle tone maturation as hypotonia improves with age (Holm et al,1993), which might mean that toileting becomes more controllable for the children with PWS. It seems likely that while the PWS children showed enuresis and encopresis, there was an organic explanation for their behaviour. The deliberate nature of soiling and urination in the HSS group implies it is a result of emotional disturbance. This finding will be discussed further below.

Sleep:

Although children with PWS were significantly more likely to have sleep cycle disruption than the children with HSS, both groups showed significantly more sleep disturbance than the stressed group. The distinction between disruption of the sleep cycle, rather than interrupted sleep is important. Some children were described as waking in the night for two or three hours during which time they would play, destroy items or eat. They then went back to sleep and woke up at the same time as their family in the morning. Other children would wake at 4 or 5 am and stay awake for the day. The behaviour was habitual and in most cases had been apparent since the child was a toddler.

Irregular sleep architecture patterns have been documented in both PWS and children who may have PSS or HSS (see 1.3.5). Guilhaume, Benoit, Gourmelen, and Richardet (1982) compared 4 'PSS' cases with healthy controls. The growth retarded children had deficits in stage IV sleep. Individuals with PWS have also been described as having deficits in slow wave sleep (stages III and IV), and a significantly lower total of REM sleep (Helbing-Zwanenburg, Kamphuisen and Mourtazaev, 1993). Though there is little evidence that shorter children have sleep disturbance in the general population (Gulliford, Price, Rona and Chinn, 1990), stage IV sleep is associated with the release of growth hormone, and children who have frank growth hormone deficiency have irregular sleep architecture (Hayashi, Shimohira, Saisho, Shimozawa and Iwakawa, 1992). This indicates that the HSS and PWS group may have some corresponding aetiology to their growth delay. However, as discussed above, the evidence for this remains debatable.

Self injury:

There were no differences between the HSS and PWS group in terms of self injury, but this finding only held if IQ was covaried. In other words, the PWS group showed

self-injurious behaviour more frequently, but when IQ was taken into account, the significant difference disappeared. In the HSSDI, no differentiation was made between deliberate skin-picking and other types of self-harming behaviour observed in abused children (eg Yeo and Yeo,1993). Therefore, the PWS affected children may show characteristic skin picking, but this is a different type of self-injurious behaviour demonstrated in stressed or abused children. Indeed, as suggested in the discussion of the enuresis and encopresis variables, it is possible that there is an organic basis to the self injury demonstrated in PWS. An organic explanation is supported by Flint and Yule (1994). However, it seems likely that there is an environmental cause to the self-injury described in HSS and stressed groups. The degree of self injury relative to the general population is uncertain, but given the existing literature concerning abused and PWS populations, it is likely that all three groups are deviant from normal children, though not significantly different from one another.

Peer relationships:

Neither teacher, parents or the children themselves, described any significant differences in HSS and PWS groups' peer relationships. Curfs (1992) suggests that there are reports of difficulty in initiating and maintaining peer relationships in children with PWS but notes that there are a lack of data to support the observation. It would be interesting to validate this finding using direct peer assessment , sociometry.

5.2.7.2 HSS in comparison to the stressed group

There were no significant differences between the HSS and stressed group in terms of general externalising, externalising at home, general attention/overactivity problems or attention/overactivity problems at home. Previous reports in the literature of overactivity, and stealing non-food items (Skuse et al, 1996) in association with HSS may be simply behaviours exhibited in many children in difficult circumstances, but should not be associated with HSS per se.

Enuresis and encopresis:

As described above, HSS and stressed children showed comparable rates of enuresis and encopresis at school, but the HSS group were more likely than the stressed children to show this type of behaviour at home. As discussed above, this

may simply be due to the likelihood of being discovered at home as compared to school, though it is possible that it is a true pattern of behaviour. Care-givers in the HSS group reported that when their child showed enuresis or encopresis, the majority of children were behaving intentionally, which indicates an environmental basis to the behaviour. Stressed children were less likely to show this behaviour at all, but of those that did, only 36% did so deliberately. It remains uncertain why the HSS group should be more likely to use enuresis or encopresis to cause an impact at home as compared to the stressed group. Previous studies describing children affected with HSS features have described such 'aggressive' patterns of enuresis and encopresis (eg Skuse et al, 1996, Money, 1977) . The finding does seem to be consistent but explanations that such behaviour is syndrome specific seem to have no theoretical basis.

Sleep:

The HSS group were reported to show nocturnal roaming. As suggested above this seems to imply sleep cycle dysfunction rather than sleep interruption. In fact sleep interruptions such as nightmares and sleep walking did not differentiate the HSS and stressed groups. As literature cited above suggests, there are physiological data to support the theory that the children with PSS (or possibly HSS see 1.3.5) have a disrupted sleep pattern. Studies of sleep architecture in a normal stressed group, in comparison to a group of children with confirmed HSS would confirm the syndrome specific nature of sleep abnormality.

Peer relationships

The stressed and HSS groups showed similar profiles of peer relationships, according to self-report, parents and teachers. Sociometry, which is a direct measure of peer relationships shows that, for example, physically abused children are less well accepted than non-abused children (Haskett and Kistner, 1991 and Salzinger, Feldman and Hammer,1993). However the abused children in these studies showed greater behavioural disturbance (despite being matched for IQ in the Haskett and Kistner study) than the non-abused group according to teachers. Children with behavioural disturbance, particularly aggression, are less well accepted by their peer group (Williams and Gilmour,1994 for review). Given that the children, in all three groups, show similarly disturbed behaviour on many variables, it is perhaps not surprising that they are equally well accepted by their peer groups.

Reports of poor peer relationships at school (Skuse et al, 1996), though they may exist, should not necessarily be interpreted as part of the HSS syndrome.

5.2.7.3 Summary

Encopresis and enuresis at home but not at school distinguished the PWS and HSS groups from the stressed group. However, the evidence suggests that the HSS children's behaviour is not organic. There was little theoretical basis to explain why enuresis and encopresis at home should be an HSS syndrome specific response. There is stronger evidence to suggest that the disrupted sleep patterns described in both the HSS and PWS groups, though significantly more frequent in the PWS group, have an organic basis. Further, nocturnal roaming was significantly less frequent in the stressed group, which suggests that disrupted sleep patterns may be an HSS syndrome specific behaviour.

5.2.8 Care-giver reported psychosocial profile (CBCL, Achenbach, 1991a)

5.2.8.1 HSS in comparison to PWS

There are 12 sub-scales covering a wide range of psychosocial functioning in the CBCL, and on each sub-scale, except thought problems, the HSS and PWS groups were indistinguishable. On the aggressive, and externalising sub-scales, the HSS and PWS groups, were as hypothesised similar to another, and distinct from the stressed group. However, in each case, the stressed group had greater adjustment difficulties. Relatively good adjustment in the HSS and PWS in comparison to the stressed group does not provide strong support for a behavioural phenotype.

The CBCL provides well standardised scores for comparison purposes. This provides evidence that the PWS and HSS groups have greater adjustment difficulties than the general population. Over 80% of the PWS and 75% of the HSS group's total problem scores were above the clinical cut-off range. Curfs, Verhulst Fryns (1991) reported that 87% of their sample of children with PWS had scores within this range, a figure very similar to the present study.

Over 50% of the PWS sample were above the clinical cut-off for thought problems, social problems, attention problems and aggression. Over 50% of the HSS group were in the same range for attention problems and delinquency (46% were in the

clinical range for social problems). It is clear both the HSS and the PWS groups are a relatively disturbed sample, but these data provide little evidence for a characteristic profile associated with the syndromes.

No age or sex influences were significant in either the PWS or the HSS profiles. Dykens and Cassidy (1994) suggested that in the PWS population aged 4 to 12 years old, there were greater adjustment difficulties in older children and boys. Their assessment questionnaire (the Reiss Scales for Children's Dual Diagnosis, 1990) was developed for children with learning disabilities but the authors do not mention whether the norms are adjusted for age and sex as they are in the CBCL. It is possible that the age and gender effects that they describe in their PWS population are expected variations in the non-PWS learning disabled population.

Dykens, Hodapp, Walsh and Nash (1992) assessed a group of 21 adolescents and adults with PWS with the CBCL, 6 of whom were in the study's youngest age range of 13 to 19 years old. They reported that this group had significantly greater externalising than internalising problems. In the present study there is a trend for externalising scores to be higher than the internalising scores but our data are not really appropriate to compare directly with the Dykens et al study. First, the present sample is rather younger than in their study. Second, the CBCL is standardised for children aged between 4 and 16, and therefore the profile is difficult to interpret for adolescents above that age range, particularly if one is relying on the CBCL standardised scores, as opposed to a comparison group, for interpretation.

5.2.8.2 HSS in comparison with the stressed group

The stressed group showed significantly more adjustment problems than the HSS group on the externalising and aggression sub-scales. The groups were not significantly different from one another on any other sub-scale. Figure 4.4.10.1 shows that proportionately more stressed children fell into the clinical range on every sub-scale except on attention problems (by a margin of only 1%) and the withdrawn sub-scale. It seems that the stressed group, according to parents, may have rather greater adjustment problems than the HSS group .However, both groups have psychosocial problems relative to the general population.

The data from the CBCL also support the suggestion discussed above in section 5.2.6, that children with HSS do not show characteristically high levels of depressive or withdrawn symptoms in comparison to the stressed group. Further as neither of the HSS group sub-scale scores reached the clinical cut-off, it might be argued that the HSS group do not have characteristically high levels of depressive symptoms or withdrawal in comparison to the general population. However though depressive symptoms are clearly not a group characteristic, 25-30% of individual children within the HSS group fell into the clinical range on these two scales.
In the stressed group but not the HSS, somatic complaints, anxious/depressed, attention problems and delinquency features all increased with age. As discussed above such age related changes may simply reflect the same behavioural pattern described in the general population. Depression and school refusal were noted to increase in adolescence by Rutter et al (1976). However, since the CBCL scores are adjusted for age and sex, this pattern indicates that, at least according to parents, the stressed group are demonstrating proportionately greater adjustment problems than their same age peers.

Watkins and Bentovim (1991) reviewed the literature on sexually abused children's CBCL profiles, and noted the following. Sexually abused children:
1) are more likely to have a total problem score in the clinical range than the normal population. In the present study, over 80% of the stressed and 76% of the HSS group were in the clinical range, as opposed to 10% in the general population.
2) have significantly elevated internalising and externalising scores. Our data show that 30% of HSS and 42% of the stressed children were in the clinical range for externalising behaviour, as opposed to 3% of the general population. 24% of the HSS and 78% of the stressed children were in the clinical range of scores for internalising problems, as compared to 3% of the general population.
3) generally show no gender difference in the degree of externalising or internalising difficulties. There were no sex effects on externalising or internalising sub-scales in the present study.

The key issue here is that the HSS and stressed profiles are similar to those described in a number of studies of sexually abused children, suggesting that such patterns might be typical of stressed children. Salzinger et al (1993) produced similar results in physically abused children. Achenbach (1991a) notes that although

abused children have elevated sub-scale scores in comparison to non-abused children, there is little evidence to show that these elevated scores are due to abuse per se, but it is accurate to suggest that elevated scores are associated with abuse. The same interpretation may be applied here. Previous studies have reported that depressive symptoms (Ferholt et al, 1985), oppositional behaviour (Blizzard and Bulatovic, 1992), social problems (Green et al, 1984) and so on are characteristic of children with HSS and PSS. Our data suggest that such psychosocial problems can be found in similar proportions in the HSS and unaffected stressed populations. Therefore these features cannot be attributed to HSS specifically. Green (1986) suggested that many behavioural features of HSS were those observed in any emotionally disturbed child. Our data would support that view.

5.2.8.3 Summary

The CBCL profiles are extremely useful as they confirm that according to parents, all three groups have marked adjustment difficulties in comparison to the general population. There is little evidence to suggest that PWS and HSS have *characteristically* similar psychosocial adjustment profiles. Comparisons between the HSS and stressed group indicate that descriptions in the literature of adjustment difficulties in children with PSS or HSS are probably a normative reaction to environmental adversity.

5.2.9 Teacher reported psychosocial adjustment (TRF, Achenbach,1991b)

5.2.9.1 HSS in comparison to PWS

There were no significant differences between the HSS, PWS and stressed groups on 10 of the 11 sub-scales in the TRF. In anxious /depressed symptomology, the PWS group was distinct from the stressed group. The stressed group showed significantly greater problems than the PWS group but was not significantly different from the HSS group. As discussed in the CBCL profiles, such a pattern does not provide evidence of an adjustment difficulty that is characteristic to a syndrome. There was a significant sex effect on attention symptomology across all three groups. As the stressed group showed such a pattern, in addition to the PWS and HSS groups, it is unwise to suggest that it is characteristic of HSS and PWS.

HSS and PWS group means were both above the clinical cut-off for total problem scores, but the stressed group were also described by teachers as similarly disturbed. 63% of the HSS and 68% of the PWS group were above the clinical cut-off score according to teachers. As suggested in the CBCL discussion, this confirms that the HSS and PWS groups have poor adjustment relative to the general population. Further, given that teachers, in addition to parents, describe both groups as having emotional and behavioural problems, it validates such a description as being representative of the children.
In the PWS group, internalising and anxious/depressed symptoms both increased with age, while there were no such age related changes in the HSS group. This indicates that according to teachers, but not parents, the children in the PWS group showed proportionately more internalising and anxious/depressed symptoms than their age related peers. There seems to be little literature which includes a standardised measure of emotional and behavioural adjustment of children with PWS according to teachers.

5.2.9.2 HSS in comparison to the stressed group

The stressed group and the HSS group were not significantly different in terms of anxious/depressed features. Therefore according to teachers, parents and the children themselves, depressive symptoms are not characteristic of the HSS group as compared to the stressed group. This provides robust evidence that growth failure in HSS is unlikely to be due to depressive symptoms as Ferholt et al (1985) suggest. All other comparisons between the HSS and stressed groups were non-significant.

Teachers, like parents, reported that both the HSS and stressed groups were rather more disturbed that their peers. Salzinger et al (1993) reported elevated TRF total problem scores, similar to the present study, in a population of physically abused children. 68% of the stressed group and 63% of the HSS group had a total problem score above the clinical range. Figure 4.4.11.1 indicates that in many sub-scales, for example externalising, anxiety/depression, social problems, delinquency and aggression, proportionately more stressed children than HSS affected children are described by teachers as scoring above the clinical cut-off.

5.2.9.3 Summary

All three groups had more emotional and behavioural disturbance according to teachers (and parents) than one would expect in the general population.
Though the HSS and PWS groups were comparable on many dimensions, their profile was similar to the stressed group. As with the parent reported CBCL data, teachers reported rather similar patterns of psychosocial adjustment in the stressed and HSS group. It would appear inaccurate to suggest that the psychosocial adjustment difficulties described in the literature (see 1.3.6.8) are intrinsic to the syndromes of HSS or PSS, as such symptomology could simply be a normative stress response.

5.2.10 A comparison of disturbance at home and school

5.2.10.1 HSS in comparison to PWS

A repeated measures ANOVA comparing CBCL and TRF sub-scale scores showed that, across the whole sample, total problem score, social problems, thought problem and attention problems were significantly higher according to parents, than according to teachers. With the exception of social problems, these differences existed to a similar degree in all three groups. However there was one significant group X context interaction which showed that there was a significantly greater discrepancy between parent and teacher reports in the PWS as compared to the HSS, or stressed groups. Caregivers in the PWS group reported significantly greater social adjustment disturbance than teachers in the PWS group. It seems that the items which contribute to the social problems sub-score (such as being clingy, or clumsy) are more pronounced according to parents in comparison to teachers in the PWS group than in the other two groups.

Both the HSS and PWS groups showed significant positive correlations between home and school appetite disturbance. This is an important validation of hyperphagia in HSS syndrome as it shows that HSS and PWS have equally pervasive hyperphagia. Hyperphagia is as significant to HSS as it is to PWS.

5.2.10.2 HSS in comparison to the stressed group

There were no significant differences between the stressed and HSS groups in the relationship between parent and teacher reported behaviour as described by the Achenbach scales (Achenbach, 1991a and b). However in both groups parents

tended to report relatively greater behavioural disturbance than teachers as described above.

5.2.10.3 Summary

There seem to be no reports in the recent literature describing the consistency of behaviours in children affected with PWS at home and at school. Such an exploration might be helpful in identifying the quality of environment which discourages problematic behaviour and encourages adaptive behaviour. Reports of hyperphagia in children with PWS are not challenged almost certainly because the affected children are often obese. In the HSS group exploring consistency of behaviour is a crucial step in establishing hyperphagia as a characteristic, pervasive feature of HSS.

5.2.11 Dysmorphology

Two dysmorphologists were presented with colour slides of the children in the PWS and HSS groups. Rater one correctly identified 87% and rater two 94% of children with PWS as having PWS. One affected HSS sibling (from a total of 24 HSS affected children presented) was wrongly identified as having PWS by both raters. Despite the blind random presentation, children with PWS were visually distinct from the HSS group. This does not support the hypothesis that children with HSS have the characteristic face associated with PWS.

The dysmorphologists commented that obesity is often used as a cue to identifying PWS. Indeed the PWS children who were wrongly identified as non-PWS tended to have relatively low BMI and the HSS affected sibling who was wrongly identified by both raters as having PWS, was relatively plump (her BMI was 1.53 sds). It would be interesting to repeat such an experiment controlling for BMI. Not all children with PWS in the present study had the syndrome's characteristic features. Butler (1990) also notes in his review of the literature that only 75% of PWS affected individuals had either a disproportionately narrow forehead or almond shaped eyes. It is not clear if both features were described in the same individuals.

5.2.11.1 Summary

Though children with HSS do not seem to have the PWS characteristic face, it is still possible that children with HSS are dysmorphic. The dysmorphologists suggested

that this was not the case, but without blind comparison against normal children, the possibility of dysmorphology remains.

5.3 Section C summary and discussion of results

The siblings

5.3.1 Familial aggregation

A total of 101 siblings (excluding index children) in the three groups were assessed using the HSS sibling checklist. A clear pattern of familial aggregation emerged only in the HSS sibling group. 30 full siblings of the HSS group index children were assessed, of those, 14 siblings fitted the HSS diagnostic algorithm. None of the siblings in the PWS group fitted the HSS criteria. As discussed in 4.5.1, one index stressed child was classified as hyperphagic using the algorithm but as he was on the 75th centile for height, he was not identified as having HSS. This child's full sibling also fitted the diagnostic algorithm, but as she was on the 50th centile for height, she was not a case either. No other children in the stressed sibling group fitted the algorithm.

The pattern of results in the HSS group, in contrast to the other groups, strongly supports the hypothesis of familial aggregation. In addition to the evidence provided by singleton siblings, there were two sets of affected identical twins[2], one pair female, another pair male who were all affected with HSS. There was a further set of male identical twins, neither of whom were affected.

5.3.1.1 The specificity and sensitivity of the HSS diagnostic algorithm

In the vast majority of cases, the diagnostic algorithm has proved accurate in identifying true cases of the condition, validated with physiological differences in

[2] the twins were identified as identical according to information provided by parents

affected versus unaffected children (Skuse et al, 1996). However there were two children in the current sample who may have been misclassified. One sibling of an HSS case narrowly missed the behavioural criteria for inclusion into the 'hyperphagic' category. He stole food habitually from home and hoarded food. If one accepts a genetic explanation, then the likelihood of this boy showing such behaviour, in addition to his having an affected sibling, indicates he probably was affected but he was classified as unaffected.

A further child, another sibling of an HSS index case may also have been misclassified. She fitted the HSS criteria as she ate excessively requiring restraint, had gorged and vomited on more than one occasion, habitually stole food at night and in the early morning from home, and hoarded food. She was below the 3rd centile in height and so she was identified as affected. However her behaviour was not entirely convincing of a true HSS case. She stole sweets, crisps and biscuits most often, rather than everyday food. A more characteristic pattern of food stealing in HSS would be to take slices of bread for example. She gorged and vomited after eating chocolates and sweets rather than savoury food. This child certainly ate everyday food excessively but the aspects of her behaviour that put her into the category of 'hyperphagic' largely involved treats and sweets. The other atypical aspect in this child's profile was that had a relatively high BMI (1.53 sds) unlike the majority of other HSS affected children. In fact she was the HSS case that was wrongly identified by the dysmorphologists as being affected with PWS (4.4.13). Clinical experience with the syndrome, rather than any objective evidence would suggest that she was not a true case, but as she fitted the algorithm, she was identified as affected.

It is crucial to maintain a strict criteria of HSS caseness if we are to establish a biochemical marker for the condition. Once the HSS classification is well established and further validated, one might look to the recent family study of autism carried out by Bolton and colleagues (Bolton, MacDonald, Pickles, Rios, Goode, Crowson, Bailey and Rutter, 1994). They suggest that it might be useful to expand the definition of the autism phenotype to a 'lesser variant', The same expansion of the HSS phenotype might prove to be appropriate in the future. However, in terms of hyperphagic behaviour in our experience to date (with the exception of these siblings) children seem to be either clearly hyperphagic or not.

5.3.1.2 The PWS group siblings

None of the siblings in the PWS group were hyperphagic according to the HSS algorithm. This provides evidence that the hyperphagia described in the affected HSS *siblings* is unlikely to be mimicry of the HSS proband's hyperphagia. If the HSS siblings were simply copying the proband, then one would expect a greater proportion of siblings in the PWS group to demonstrate similar behaviour. It might be argued that because the child affected with PWS is labelled as having 'a condition', the siblings in the family may be less inclined to imitate behaviour. However many of the index children with HSS have had numerous investigations and hospital admissions, and are similarly labelled as having 'a condition' in the family.

Further we have unpublished data collected through a postal survey of children who fitted the hyperphagia criteria according to parental report, but have not been diagnosed as having any condition. These undiagnosed hyperphagic children's nearest age siblings were not hyperphagic either. Alternatively one might suggest that in the PWS group families, having hyperphagia equates with getting attention from parents. Despite such a potential secondary gain, none of the siblings in the PWS group demonstrated behaviour fitting the criteria. It seems that siblings are disinclined to mimic hyperphagia. If one considers the nature of behaviour described in the criteria for hyperphagia, it seems feasible that siblings do not regard it as particularly attractive behaviour to copy, for example eating until vomiting, foraging in dustbins or waking in the night to eat.

5.3.1.3 The stressed group siblings

It is intriguing that of the 53 children (25 index children, 19 full, 6 half and 3 unrelated siblings) assessed in the stressed group, the only two children who fitted the hyperphagic algorithm (but not in terms of stature) were full siblings. As discussed above, the index child was on the 75th centile, and his sister on the 50th centile and so neither were affected with HSS. One might speculate that these children demonstrated a variant of HSS (see 4.5.1.1). However that the only children who were hyperphagic were full siblings supports the idea that hyperphagia as a stress response has a genetic basis. There are two studies that report hyperphagic children who are not all of short stature (Demb, 1991 and Ayoob et al,1994). There were two sibling pairs in each group of 10 and 13 children respectively. In each case

the siblings were not living in the same home, making imitation an unlikely explanation. As discussed in the introduction (see 1.4.2.4) we cannot certainly exclude HSS in these studies as height velocity may have been retarded. The same argument may apply here for the two children in the stressed group.

5.3.1.4 The mode of inheritance

None of the half siblings in either the PWS or stressed groups were affected. Of 15 half siblings assessed in the HSS group, only one was affected. This child shared the same mother with the proband, but their fathers were brothers. If we accept that HSS may be a recessive trait, the affected children's mother and father must both have been carriers. The brother of the proband's father has a 50% chance of being a carrier too. This pattern, together with the data on the full sibling reoccurrence rate is strongly suggestive of a recessive mode of inheritance, though the recurrence risk in the HSS families is rather higher than one might expect in recessive inheritance. There was no evidence of an uneven sex ratio when affected siblings in the HSS group were compared to unaffected siblings. This finding held when full siblings only were compared. Though the findings seem to indicate a recessive trait, this is the first study to document the HSS incidence rate in families, and the sample is small, so it might be unwise to draw any firm conclusions about the mode of inheritance.

5.3.1.5 Family studies

Family studies can provide data which support the hypothesis of genetic influences but they cannot provide evidence to the degree of certainty that genetic markers or even twin studies could. Twin studies would be rather difficult to carry out, since the syndrome is relatively rare (Skuse et al, 1996). The confounding factor in family studies is that families share environments as well as genes, therefore similarities between family members could be due to the similarity of their experiences in that family. Similarly those who are apparently 'unaffected' may just have had a different experience with the same family. However where the transmission pattern follows Mendelian inheritance (as it seems to in the present study), environmental explanations are less probable (Lombroso, Pauls and Leckman,1994). Our data fit a genetic explanation, in the context of a stressful environment, more accurately than a purely environmental one. Further Rutter, Bolton, Harrington, Le Couteur, MacDonald and Simonoff (1990) note that when the environmental risk factor for a genetic condition is known, that risk factor can be controlled in the family study. Any

effect found thereafter is more likely to have a genetic explanation. We have identified at least one environmental risk factor (stress) and have controlled for it accordingly.

It makes intuitive sense that there may be a biochemical, and therefore almost inevitably ultimately a genetic mediator to explain why the children with HSS apparently react in a specific manner to such a common environment. However, the possibility remains that there is a specific aspect in the HSS affected children's environment that triggers the syndrome. The evidence we have provided would not support such a theory, but more intensive study of the children's environment and perception of that environment would validate a genetic explanation, in the absence of biochemical markers.

In taking the purely environmental explanation further, one might consider the affected versus unaffected siblings' respective environments. As we did not gather any data such as Expressed Emotion ratings on the siblings, we can't be certain that there were not subtle qualitative differences in their environments. However there are a number of important points that should be made.

First, we might predict that the same subtle variations in the quality of the stressful environment would exist for stressed index children and their siblings, yet none of these children manifested the condition. As discussed in 1.5.3.5, there is evidence that *previous* experiences may affect the type of future stress response that rats (Wiener and Levine,1983) or non-human primates (Coe, 1993) will show. It seems counter-intuitive that such experiences, for example separation or neglect, were not evident in similar proportions in the stressed children and their siblings. Retrospective accounts of the index children's experiences certainly did not indicate any specific experiences in infancy in the HSS group as opposed to the stressed group. Further it seems most unlikely that only full siblings, but not half siblings were systematically exposed to specific experiences in the past.

Second, there were four half siblings, all unaffected, who were removed from home with the proband following social services involvement. If a child's genetic predisposition is not partly responsible for the HSS syndrome, then why didn't more half siblings manifest the condition ? The half siblings were judged by social services

to be similarly stressed or 'at risk' as their affected half siblings. Using conservative judgement a further 6 full unaffected siblings were identified by professionals to be living in the similar psychosocial adversity as their affected siblings. The child AS, who seemed to manifest her condition following civil war and countless relocations had two unaffected siblings who had lived through the same experiences.

Third, one could argue that simply being in a family in which there are social service investigations or psychosocial concerns, by definition, means that all the siblings living at home were living in comparable conditions of chronic stress.

5.3.1.6 Summary

Family studies, though they may disprove genetic influences in a controlled study, cannot conclusively prove a genetic basis. Bearing this caution in mind, the evidence from the present study provides strong support for the hypothesis that HSS shows familial aggregation indicative of a genetic basis. Where one child is affected with the condition there is a significantly greater likelihood that another sibling in that sibship will demonstrate the phenotype as compared to the PWS and stressed group siblings. Further, the segregation pattern fits a recessive mode of inheritance.

5.3.2 The independent indicators of HSS

In order to validate the distinct nature of the HSS syndrome, three indicators, independent of the HSS diagnostic algorithm were explored. For these analyses only the HSS group index children and their siblings were compared with one another on the basis of their affected status.

5.3.2.1 Cognitive ability

Full scale, and performance IQ scores were significantly lower in children affected with the HSS condition as compared to their unaffected siblings. Though verbal IQ tended to be lower in affected as compared with unaffected siblings, it was not significantly different. Performance IQ is regarded as an index of ability (Kline,1991) while verbal IQ at least in the WISC-R (Wechsler, 1974) is a 'reasonable' (pp239) measure of attainment (Yule, Gold and Busch, 1981 and Kline,1991). This suggests that the HSS affected children's cognitive *potential* might be influenced, rather than just their achievement level.

In section 5.2.2.2, the non-significant difference between the stressed and HSS index children's IQ was discussed. That comparison could not provide evidence that cognitive deficits are associated with HSS specifically. The analysis comparing affected and unaffected siblings in the same family groups is rather more informative than comparing the stressed and HSS groups, because family group was entered into the analysis. By examining the effect of family group, we can, at least to *some* degree, take into account differences in the quality of shared family environment, and genetic influences independent of HSS. Both environmental and genetic factors influence IQ scores (eg Rutter, 1985c). Further there are gene environment interactions (Plomin, Defries and Loehlin, 1977) which have additional effects on IQ. For example, a family in which a parent has a learning disability (genetic influence) may provide an inadequate environment in terms of cognitive simulation for the child (gene environment correlation) in addition to living in an area that has a school which has a poor educational record (environmental influence). The analysis cannot take into account environmental experiences peculiar to that child, though twin studies suggest that such non-shared environmental influences on IQ are relatively small accounting for about 14 % of the variance, (Brody,1992 for review). Nor can it quantify the proportion of shared genetic and environmental factors that affect cognitive ability or any other outcome variable.

5.3.2.2 Psychosocial adjustment

In total problem score, internalising, externalising, withdrawn, social problems, thought problems, attention problems, delinquency and aggressive behaviour, the affected children showed significantly poorer adjustment than their unaffected siblings. Though there was no significant difference between the affected and unaffected siblings in the HSS group for somatic complaints, anxious/depressed and sexual problems, the group means showed trends in the same direction as before.

Much of the 5.2 discussion suggests that many of the psychosocial adjustment problems described in children with PSS or HSS in the literature may simply be non-specific reactions to environmental adversity. We would argue that this conclusion is still supported, because although these analyses are showing significant differences in adjustment between affected and unaffected siblings, there are two important points to note. First these analyses do not hold IQ constant, and the differences in adjustment may be attributed to the significant differences in cognitive ability

described previously (Goodman et al, 1995) . Second the affected children's group mean scores, with the exception of total problem and attention problems, are not in the clinical range. This suggests that though the affected siblings are poorly adjusted relative to their unaffected siblings on many of the problem sub-scales, the differences between affected and unaffected are not equivalent to the adjustment 'divide' between the 'normal' and disturbed population.

5.3.2.3 Birthweight

This analysis was limited as the numbers of affected and unaffected siblings that were compared were extremely small, and so reducing the power of the comparison. The analysis indicated that birthweight was unaffected by affected status. Comparisons between the stressed and HSS index children would also support the theory that the HSS syndrome has no effect on birthweight . However it should be noted that the comparisons between the stressed and HSS groups might be viewed as weaker than the analysis between siblings affected and unaffected with HSS . As discussed above, this analysis does take into account some (though certainly not all) aspects of the 'normal' genetic influences such as maternal height, independent of HSS on birthweight.

Evidence that suggests there are infant health markers that pre-date the manifestation of HSS, such as failure to thrive or hypotonia, might lead one to suspect that birthweight may indeed be affected in HSS. More extensive investigations using objective data are warranted in order to explore that theory.

5.3.2.4 Summary

The evidence that children affected with the syndrome have significantly lower full scale and performance IQ scores than their unaffected siblings is important. It indicates that HSS may have non-environmental, in other words genetic, components. IQ scores were measured using direct assessment and therefore free of potential parental reporting bias. Further performance IQ is probably affected by environmental influences to a lesser extent than verbal IQ (Rutter, 1985c), though it is certainly not free from environmental effects.

Critics such as Kreiger,(1974) have suggested that children affected with HSS are simply being starved, so the children are apparently 'hyperphagic', and therefore stunted. Following that line of argument, one could argue that the lower IQ scores in

the children affected with the syndrome as compared to those unaffected, were a result of scape-goating and poorer stimulation in the family. However if that were the case, then one would expect to see verbal IQ significantly lower in affected children as compared to unaffected, because it is probably shaped by the environment to a greater degree than performance IQ (Rutter, 1985c). The issue of cognitive deficits in association with HSS is an important area of investigation requiring replication with larger sample sizes and a more extensive neurospychological test battery.

Rutter et al (1990) note that comparisons between affected and unaffected siblings can highlight non-shared influences, both genetic and environmental. The method cannot identify the nature (genetic or environmental) of those non-shared influences. An extended investigation on all of the HSS specific dimensions described in the present study of affected and unaffected siblings would be most informative. For example, the HSS sibling check-list included a question about waking frequently in the night. Evidence from the data in the HSSDI interview comparing the stressed and HSS children indicates that waking in the night does not differentiate the HSS and stressed groups, but nocturnal roaming does. The check-list question was not specific enough. It was important to ask about sleep interruption such as night mares and so on, but a more informative line of inquiry would have, in addition, included questions about sleep cycle disruption.

5.4 Section D summary and discussion of results: Molecular genetics

5.4.1 Methylation studies

All 14 children affected with HSS, tested using the PWS diagnostic methylation status test, showed a normal methylation pattern at 15q11-13. This methylation test demonstrates a characteristic pattern of allelic expression in 99% of PWS cases who have either a deletion (70%), uni-parental disomy (28%), or in very rare cases a methylation mutation (2%) (The American Society of Human Genetics,1996). In tests with the PW71b probe (Dittrich et al, 1992) for example, individuals affected with PWS show only the maternally derived 6.6kb fragment and lack the 4.7Kb fragment derived from their father. None of the HSS affected cases showed this pattern.

5.4.2 Linkage Studies

Two pedigrees were examined using four CA repeat markers (Mutirangura et al,1993) which cover the length of the PWS critical region. There was no recombination between the markers in family M and it is highly unlikely in family C, though possible in the maternal allele, suggesting that the PWS critical region of chromosome 15 were transmitted intact.

Dominant transmission:

If the HSS locus had been located in this region, one would expect that the affected siblings within a family would show the same pattern of allelic inheritance consistently on either the maternal or the paternal allele, while the unaffected siblings would show a different pattern.

Recessive Inheritance:

The pattern of familial aggregation is suggestive of recessive transmission. If that were the case, then one would expect that the affected siblings within a family would show the same pattern of allelic inheritance on *both* alleles, while the unaffected siblings would show a different pattern.

Neither pattern was apparent in the pedigrees, making linkage at the PWS critical region highly unlikely. It is possible, in theory, that there was recombination in both families but as the markers are tightly linked to the region, the probability of both families showing recombination is extremely small.

5.4.3 Summary

Both the methylation and linkage studies support the same conclusion. The methylation studies exclude anomalies associated with PWS at 15q 11-13 in HSS but do not exclude point mutations of the region, for example. The linkage studies are rather more powerful as they exclude the PWS locus altogether. It is highly unlikely that the loci associated with HSS and PWS coinherit.

5.4.4 Future genetic investigations

There are striking similarities between the PWS and HSS syndrome phenotypes, which made testing the relationship between the HSS and PWS genotype important.

However it is perhaps unsurprising to find that children affected with HSS show no anomalies at 15q11-13. The HSS features have the potential to resolve when an affected child is separated from the stressor. The PWS features are permanent. Further, the features of HSS will reappear if an affected child is reintroduced into a stressful environment after having been separated from the stressor and recovered. This suggests that the HSS condition has a complex mechanism underlying it.

Because the syndrome seems to switch on and off in response to environmental cues, it seems possible that DNA regulatory sequences which control the expression of structural genes might be involved in HSS. Genes are expressed in different tissues and expressed at specific stages in development in response to different regulatory sequences (Rosenthal, 1994), therefore genes expressed or suppressed, in response to a particular environment, are theoretically possible. Or, more likely there may be a low level of gene expression, which increases in response to the environment. The environment which we have suggested triggers the HSS gene expression, is essentially one in which the child is threatened, a situation which results in many dramatic physiological changes in the normal population. In this context, suggesting that genes may switch off or on or increase in expression in response to long-term threat is not too far-fetched. Alternatively the HSS gene(s) expression may be constant, but as a direct or indirect result of that genotype, an affected child shows an abnormal response in conditions of severe and chronic stress.

Candidate genes:

Genes involved in the expression of neuropeptide Y and its receptors and GLP-1, because of their involvement in appetite control (eg Morely, 1987, Turton et al, 1996), are candidates for HSS, in addition to genes involved in the regulation of the hypothalamus. There are also variety of genes that have been mapped that are involved in growth regulation which deserve investigation. For example, the *lit* mouse is growth retarded, which does not respond to exogenous growth hormone and so may be regarded as a potential mouse model for HSS. The *lit* mouse has a mutated GHRH receptor gene which has been mapped to chromosome 6 (Mayo, 1996). An alternative mouse model for HSS was recently described by Cummings et al (1996). This mutant mouse strain can eat excessively without gaining weight but when eating a more appropriate calorie intake, continues to maintain a normal BMI. Finally, de

Vries et al (1993) describe a series of Fragile X patients who have many features of the PWS phenotype and the HSS phenotype, such as short stature, obesity secondary to hyperphagia and learning difficulties. Because it is X linked and so more prevalent in males, it is a rather unlikely candidate as HSS shows no sex bias (see 4.5.1) but perhaps one that should be excluded.

Cytogenetic studies:

The molecular genetic investigations in this study tested a specific hypothesis - the coinheritance of the HSS with the PWS loci. While it is important to have an explicit hypothesis, it means that other genetic strategies have not yet been explored. To our knowledge there have been no other investigations into the HSS phenotype. As described above we have a number of candidate genes for HSS. In addition to these explorations, it is important to carry out a cytogenetic examination of the chromosomes in a series of affected children. There may be a chromosomal anomaly associated with HSS. For example there may be a rare translocation which may act as a linkage 'clue' for a mutant gene. However, the evidence suggesting recessive transmission makes cytogenetic studies less of a priority.

A single gene disorder?

An alternative theory is that HSS is not a single gene condition, but a polygenic disorder. Psychiatric conditions, or at least those in which there is a psychosocial component such as schizophrenia, are generally suspected to be polygenic (Rutter, Bolton, Harrington, Le Couteur, MacDonald and Simonoff, 1990, Belmaker,1991). Cloninger, Adolfsson and Svrakic (1996) note that recently specific loci for human personality have been mapped, suggesting that even the most complex of traits such as personality, may be mapped to specific sites on the genome. This is not to say that all the variance in an aspect of personality due to genetic factors can be explained by the variation at one locus.

A model for investigating complex conditions:

The model and procedure necessary to map the gene 'responsible' for fixed phenotype single gene disorders such as Huntington's disease are well established - though actually mapping the genes is certainly not guaranteed. Complex disorders in which there is a direct genetic aetiology are less well investigated. Mapping the gene or genes associated with HSS might serve as a model for research into other multi-

dimensional genetic conditions, in which environmental, psychosocial and neuroendocrine factors closely interact.

5.5 General Discussion and overview

5.5.1 The summary table of results

The table below high-lights the similarities and differences among the groups in tabular form.

Table 5.5.1.1: The results summary

feature	*HSS*	*PWS*	*stressed*
psychosocial adversity and stress	yes	no	yes
severe learning difficulties	no	yes	no
performance vs verbal IQ discrepancy	often	rarely	often
short stature	yes	yes	no
high BMI	no	yes	no
weight gain probs in infancy	often	yes	no
hypotonia in infancy	sometimes	yes	no
delayed milestones	no	yes	no
hyperphagia	yes	yes	no
polydipsia	yes	no	no
internalising problems	yes	yes	yes
externalising problems	yes	yes	yes
self injury	yes	yes	yes
sleep disruption	yes	yes	no
deliberate enuresis/encopresis at home	yes	no	no
dysmorphology	unlikely	sometimes	n/a
familial aggregation	yes	extremely rare	no
anomaly at 15q11-13	no	yes	n/a

5.5.2 Summary of results

5.5.2.1 Section A :stress, parenting style and family environment

Systematic measurements of the Expressed Emotion (Vaughn, 1989) surrounding the index children in our study showed that both the stressed and HSS children experienced a similar 'emotional temperature' (Vaughn, 1989) from their care-taker. This, in conjunction with evidence in the literature that high EE relatives are 'emotionally arousing' (Vaughn, 1989) strongly supports the theory that HSS is a stress responsive condition. Data gathered from external sources such as social services and other mental health professionals validated the hypothesis that the HSS group and stressed children were living in comparable psychosocial adversity. There was no evidence from these investigations that children with HSS were experiencing a characteristic type of stress (such as sexual abuse) in comparison to the stressed children. Data from self reported family environment descriptions show that the HSS and stressed group families are characteristically 'disorganised'. Disorganised families are associated with psychosocial adversity (Long and Jackson,1994). The remaining results from the Family Environment Scale did not disprove the theory, but did not validate it either. Similarly attempts to document the degree of stress experienced by each of the groups using measures of HPA response and reactivity were not informative as the results were inconclusive.

5.5.2.2 Section B: The HSS phenotype

Numerous investigations of psychosocial adjustment, infant health, cognitive ability and anthropometric characteristics were described in order to identify those features in HSS which were 'syndrome specific' (Flint, 1996) and those which were most likely to be normative stress responses. Short stature, failure to thrive and poor muscle tone in infancy, hyperphagia and appetite disturbance, sleep cycle disruption (as opposed to interruption) and deliberate enuresis and encopresis at home differentiated the stressed and HSS groups convincingly. Sleep appetite and growth are influenced directly or indirectly by hypothalamic nuclei (Fix,1995). This neurological correlate may be regarded as further evidence that HSS is a valid syndrome.

Though there was evidence that the HSS children were disturbed in terms of their emotional and behavioural adjustment on many variables in comparison to the general population, their profile was similar to the stressed children. This indicates that such externalising and internalising problems may be normative response to an adverse environment.

Comparisons between the HSS and PWS group, in order to examine the parallels in the respective syndrome phenotypes, showed a number of similarities and differences. Children affected with PWS and HSS were both of short stature in comparison to the general population, though HSS to a greater degree than PWS. Both groups were significantly more likely to fail to thrive and have poor muscle tone in infancy than the stressed group, but the PWS group in both instances showed more severe difficulties than the HSS group. If we define hypotonia as poor muscle tone that was identified by medical professionals, then the PWS children are clearly affected more frequently than the HSS group. Both groups showed comparable appetite disturbance in terms of degree, quality and consistency of behaviour at home and school. However while HSS children were described as polydipsic, the PWS group children were not. PWS and HSS had equivalent sleep patterns. There are sleep architecture studies described in the literature to validate our study's parental reports (eg Guilhaume et al , 1982 and Helbing-Zwanenburg et al,1993). Further, each group was described as showing enuresis and encopresis at home, and there were also frequent descriptions of self-injury. It was concluded that the PWS group's behaviour had an organic explanation, while the HSS affected children's behaviour was more likely to have an environmental basis. There was evidence to suggest that both groups were disturbed in terms of their psychosocial adjustment relative to the general population, but the parallels were probably not characteristic of both the syndromes.

PWS and HSS affected children were distinct from one another on a number of dimensions. HSS children had significantly higher cognitive ability, and a distinct profile of cognitive strengths in comparison to the PWS group. The HSS group was more likely to show a significant discrepancy between performance and verbal IQ. In the children who did show such a discrepancy, the HSS children were more likely to have superior performance skills while the PWS children were more likely to have superior verbal skills. The PWS group showed a significantly higher BMI in contrast to the HSS group mean. The HSS group BMI mean was very close to the general population mean. Finally there was no evidence that the HSS group had the characteristic PWS-like facial features, though it is also true to say that many of the PWS group children did not have the 'characteristic PWS face' either.

5.5.2.3 Section C: the siblings

There was evidence of familial aggregation of the HSS syndrome in the HSS group but no HSS-like children were seen in the PWS or stressed groups. Two sets of identical twins, one male pair and one female pair were affected. A further set of male identical twin brothers of an HSS proband were both unaffected. PWS siblings apparently did not mimic the behaviour of the PWS proband in their family, making it unlikely that the affected siblings in the HSS families were imitating the HSS proband in *their* family. Two full stressed siblings fitted the HSS hyperphagia behavioural criteria, but were not of short stature.

All affected children were full siblings (according to parental report) of the proband, with one exception. This child shared the same mother with the proband and their fathers were brothers. There was no significant distortion of sex distribution in the affected siblings. Such a pattern suggests a recessive mode of inheritance, though the recurrence rate was higher than one might expect in a recessive disorder.

Affected and unaffected siblings in the HSS group were compared. Taking into account intra-familial correlations, affected children showed deficits in full scale and performance IQ in comparison to their unaffected siblings. It has been suggested that performance IQ may be less affected by environmental influences than verbal IQ (Rutter, 1985c) , which did not differentiate the groups. This might mean that HSS affected children's cognitive potential is affected. There were differences between affected and unaffected siblings' reported psychosocial adjustment, but these may be attributed to the differences in affected and unaffected siblings' IQ scores. Further many of the differences were between scores within the normal population range, as opposed to across the clinic referred population score threshold. Birthweight failed to differentiate the affected and unaffected siblings.

Though a family study can not prove genetic influences conclusively, the data in the current study fit a genetic model better than a purely environmental one.

5.5.2.4 Section D: Molecular genetics

Methylation pattern tests and sibling pair linkage studies at 15q11-13 almost certainly disprove the theory that any major locus associated with HSS coinherits with the PWS locus. Though there were similarities in the PWS and HSS

phenotypes, the potential for the HSS features to resolve in response to the environment, does not exist in PWS. The reversibility issue led to speculation that there may be DNA regulatory sequences involved in the switching on and off 'the HSS gene'. Polygenic explanations for HSS are also possible. Candidate gene testing and cytogenetic studies should be carried out on the HSS affected population.

5.5.3 Limitations and comments

5.5.3.1 Subjects

Parental report

Much of the present study relies on parent and teacher reports to construct the children's psychosocial profile. Most paediatric psychological and psychiatric assessment and intervention relies on parental report. However, for some variables such as sleep patterns, activity level or calories consumed, there are direct and objective measures available which would provide more detailed and perhaps more valid information. Future research might aim to employ these methods.

Many of the parents in the HSS and stressed groups were suspected, at least, of being abusive towards their children. We need to consider how reliable a source of information these parents may be. There is no evidence to support the idea that abusive parents provide less valid descriptions of their child's behaviour than non-abusive parents, and they do have accurate parenting knowledge (Friedrich and Wheeler,1982). Indeed anecdotally the impression is often that the abusing families are only too happy to describe their child's behaviour whether socially acceptable or not. This may be because abusing parents minimise their own contribution to their children's difficult behaviour (Bradley and Peters,1991). In other words, abusing parents tend to externalise the reasons behind their child's behaviour, rather than reasoning that it may be due to their own parenting. It is rather more questionable whether abusing parents should be regarded as a valid source of information concerning their *own* behaviour towards their children.

Another point which may increase confidence in the parents' report is that we met with the families in a research context. We asked for their help, to give us information about child behaviour patterns and appetite, rather than as a clinician gathering

information on a family difficulty. There is no inference in a research setting that parents are responsible for a presenting problem, or indeed that the families have a problem at all. This may have encouraged families to provide less censored information.

That many of the care-givers were suspected of abuse does raise concerns, as discussed above, but at the same time it is crucial that such a population was involved in this study. These extreme groups provide 'ecologically valid' information because they are representative of families in distress.

Sampling bias

All the families in the stressed group were receiving input from professionals, either from social services and/or from EBD schools. Could this factor bias the study's findings in any way? One possible interpretation, is that the stressed children, having been referred to a professional body must be relatively more disturbed than non-referred groups to have been identified at all. If this is a fair rationale, and one is arguing that hyperphagia is simply an extreme normative response then one would predict that children in the stressed group would be hyperphagic. In fact 68% of the HSS group also had psychosocial professional input. Therefore any other possible concerns of bias due to professional contact is relatively well balanced by the HSS group.

A normal comparison group.

Where standardised instruments were used, all three groups were, as expected deviant from the general population norm on most variables. However, normative data on the HSSDI and CAS, for example would strengthen the validity of the findings.

5.5.3.2 Measures

Multiple sources:

Using multiple sources in order to construct children's psychosocial adjustment profiles was vital. Both teachers and parents 'agreed' that HSS affected children were significantly more hyperphagic than stressed children, for example. Parents, teachers and the children themselves, largely described similar patterns on many of the psychosocial variables which failed to distinguish between groups. In other

words, there is consensus validation of the behavioural profile of the three groups relative to one another in many cases.

Multi-disciplinary investigations:

Using a multi-disciplinary approach is crucial, particularly when investigating a condition such as HSS which has psychosocial, physiological and almost certainly genetic dimensions. Each type of investigation can inform another. Although in the present study we failed to validate the 'psychosocial' hypotheses with molecular or physiological data, it was important to attempt this cross-validation. Where two disciplines produce complementary findings from different perspectives, the results are extremely robust.

Unstandardised measures (the HSSDI)

Flint (1996) notes that validating assessment tools to measure behaviour that is associated with rare syndromes is difficult *because* of the rarity of the condition. He makes an important point by suggesting that by using standard assessment tools, unique behaviours may not be documented. The correct questions need to be asked and very rare behaviours are unlikely to be included in standard instruments. The HSSDI was developed to identify the condition, precisely because there was no existing measure to describe the features of HSS. Further, its validity in identifying true cases of HSS, who are physiologically distinct from non-cases has been described (Skuse et al, 1996).

5.5.3.3 Design

Developmental patterns and the natural history of HSS.

By using cross-sectional data, age related changes rather than developmental trends were described. Because each child in our study had their own experience of similar stressors, it is not possible to comment with confidence on age related patterns in response to stress. Increasing age and cognitive development may act as a risk or as a protecting factor in conditions of stress as Yule (1994) speculates. There is some evidence that younger children may have fewer cognitive (but not fewer behavioural) coping strategies in stressful situations as compared with older children (Altshuler and Ruble, 1989) suggesting younger children may be more vulnerable in

some situations. However much of our data, particularly in the stressed group, showed increased symptomotology with age. The children's age range in the present study covers the onset of puberty and adolescence, which is associated with a small relative increase in behavioural and emotional difficulties in the normal population (Rutter et al,1976).
Longitudinal data would be most informative in cases where a child affected with HSS is separated from the stressor, for example, in order to monitor the correlation between the degree of behavioural disturbance resolution and the quality of the child's environment. It might be that the features specific to HSS (which are largely physiological) may resolve very rapidly, while the non-specific and largely psychosocial features are more enduring.

What is the natural history of HSS? Currently, we can only speculate. The oldest individual affected with HSS in childhood, and with whom we still have contact, is now twenty years old, described in a previous study of HSS cases (Skuse et al, 1996). He continues to have behavioural adjustment problems, but no longer demonstrates the HSS behavioural phenotype. He is living independently and in a relatively stress-free environment, as far as we can ascertain. We don't know how adults affected with HSS might react in conditions of stress such as domestic violence.

We asked all biological parents of children affected with HSS about their behaviour and stature in their own childhood. Three parents (one mother ,CN and two fathers, RC and SD) of HSS cases described being affected themselves in childhood, on the basis of their retrospective accounts. For example, RC described drinking vinegar and from streams and stealing food from cupboards in the children's home in which he periodically lived. He also reported being the shortest in his class at school. All three described abuse in their childhood. RC and SD reported physical abuse, CN sexual abuse from her own father.

As adults, these three parents were not significantly shorter than the HSS parents who described themselves as being unaffected in childhood. CN measured 154.94 cm compared a mean of 157.51cm in the 'unaffected mothers' group ($t = 0.51$, $p = 0.62$). RC and SD's mean height was 165.10 cm as compared to 167.11 cm in the 'unaffected fathers' group ($t = 0.48$, $p = 0.66$). None of the three parents reported

being hyperphagic as adults. The degree of stress in their current environment was not assessed, though one might suggest, since social services were investigating their parenting in two cases, their circumstances were not optimum. Because retrospective data into one's own childhood are potentially so unreliable without corroboration, they were not presented in the results section, but it does suggest a systematic longitudinal study is warranted.

It is possible that HSS is simply a childhood condition, with no equivalent adult manifestation. If we hypothesise that HSS is associated with a single gene, which is turned on or off by DNA regulatory sequences, it is feasible that the 'HSS' gene switches off at a specific time in development, once growth is complete, in adulthood. Alternatively, adults affected with HSS in childhood may continue to show some features. Delayed growth rate is, of course, only applicable in childhood, but there may be a drop in growth hormone production in response to stress in adulthood. Growth hormone insufficiency in adulthood correlates with mood disturbance and fatigue (McGauley,1989, Lieberman and Hoffman,1996). Hyperphagia as a stress response may continue throughout development into adulthood, but there is no evidence as yet to support these speculations.

5.5.4 Stress: a problem of definition

Individual differences in reactivity

Any attempts to claim that we have systematically measured the degree or quality of stress *experienced* by the children who took part in this study would be inaccurate. What we have attempted to do is measure aspects of the children's environment which may be regarded as stressful. For example, we used social services criteria and assessed main care-giver's emotional response towards to the child by Expressed Emotion. It is not feasible to control for each child's own individual interpretation of that stressor, which will mediate any stress response. Indeed Gerlsma, van der Lubbe, and van Nieuwenhuizen (1992) suggested that a (in our case) child's perception of the expressed emotion directed at them might allow greater predictive validity than simply the EE rating alone. The same event may be attributed in diverse ways by different children. For example some children may attribute the cause of a traumatic event as external (an explanation involving other people or other events), while others may use an internal attribution (an explanation involving the child) for the same event (Joseph, Brewin, Yule and Williams,1993).

As suggested in the introduction, an individual is stressed when ' the demands made on them exceed the capacity to meet those demands' (Yule, 1994, pp396). Abuse or neglect within the family certainly would exceed most children's coping resources. The literature shows that intra-familial abuse or neglect has more severe consequences on children's adjustment in the short and long-term when compared to children abused by acquaintances. Further, chronic as opposed to acute stress (or abuse) is associated with greater disturbance (Sirles, Smith and Kusama, 1989). On that basis, it may be that since the majority of the stressed and HSS children experienced chronic abuse (confirmed or suspected) from a care-giver, we may be relatively certain that these children were *experiencing* severe chronic stress, rather than simply being exposed to a stressor. The fact that children affected with HSS show recovery when separated from the stressor, further validates that the children were indeed experiencing chronic stress previous to the separation.

It may be argued that an individual's 'interpretation' of physical, as opposed to psychological stress can be objectively measured, using pulse rate for example. In the present study, an objective measure of an acute physical stressor failed to be informative. It is possible that in order to be discriminating, the physical stressor must be so challenging to the child that the procedure would not be ethically acceptable.

Selecting the stressed children from environments previously established to be associated with HSS is an important initial step in disproving the theory that HSS is a normative response. More systematic inquiry into duration, individual children's coping strategies and perception of the stressful circumstances is required. Another future investigative route could involve using more sensitive physiological measures, in order to match more closely the degree of stress experienced by children.

PWS: a stressor.

Having a child in the family with Prader-Willi syndrome is stressful, for parents and siblings, an issue raised by James and Brown, (1993). The condition impinges on the family in many ways, for example influencing the type of food available in the household. Children are often required to 'excuse' their PWS affected siblings' socially unacceptable behaviour. Children who are affected with the condition must also be regarded as stressed. With increasing evidence that individuals affected with

PWS have a delayed satiation response, and do actually feel hungry more promptly after eating than comparisons (Holland, Treasure, Coskeran and Dallow, 1995, Holland, Treasure, Coskeran, Dallow, Milton and Hillhouse, 1993), it is hardly surprising that they are distressed. In some cases affected children may lack the cognitive capacity to understand why they should not eat until satiated, exacerbating their distress.

We would argue that the stress experienced by children and families in the PWS group is qualitatively different from the HSS and stressed groups, because in the PWS context, the source of stress is not 'active' or personified. In other words, in PWS the condition is the stressor, rather than an abusing or neglecting parent, for example. This is not to imply that abusive parents are invariably deliberately abusive or 'to blame' for their behaviour, but simply that there is a person (or persons) directly associated with, or causing, the stressful situation. Yule (1994) reports that stress which is caused deliberately results in increased distress as compared to accidental events. One might guess that from the abused child's perspective the abuse is deliberate.

5.5.5 The HSS Phenotype

HSS: A syndrome or a phenotype or both?

A syndrome is defined as ' a distinct group of signs and symptoms which, associated together, form a characteristic clinical picture' (Butterworth's Medical Dictionary,1978). Certainly HSS would seem to fit that criteria. Discussing the HSS 'phenotype' as being synonymous with the syndrome implies that a genetic basis has been confirmed. The findings from this study strongly support a genetic predisposition, but until there is a marker at a molecular or chromosomal level, there remains the possibility that describing HSS as having 'a phenotype' is inappropriate.

5.5.6 Genetic issues and explanations:

5.5.6.1 Qualitative and quantitative differences

Rutter (1994) debates at what point one should regard a condition as qualitatively different from the general population or simply the extreme end of the distribution. He uses learning difficulties as an example. Mild, but not severe, learning difficulties are largely regarded as abilities that are at the far end of the normal distribution. This is because children with a learning disabled sibling show regression to the mean in IQ, while siblings of a child with severe learning difficulties do not. In other words, the

process (or group of genes) resulting in mild learning difficulties also produces abilities in the average and above average range. In contrast, it is more likely that the process (or genes) resulting in severe learning difficulties is distinct from the 'usual process'. This illustrates that the same behaviour at different levels of severity can have separate mechanisms.

This neat differentiation relies on a meaningful reference point for defining the severity of learning difficulties. Such a differentiation is more difficult when discussing growth - the degree of growth retardation in the child is not a helpful definition of the severity of growth disorder because the length of exposure to an environment also dictates the degree of growth retardation. However, growth and IQ are both quantitative traits, which draws a parallel between learning difficulties and growth retardation. If we apply this idea to HSS, we might suggest that HSS is a qualitatively distinct stress response, with a distinct mechanism and aetiology causing the growth failure (the equivalent of severe cognitive deficits described by Rutter). The other environmentally induced growth retarding syndromes described in the introduction might be regarded as being driven by the growth mechanism in the general population, in the same way that milder cognitive deficits are regarded as being on the same continuum the general population.

5.5.6.2 Gene environment interactions:

Scarr and McCartney (1983) note that an individual's genotype will affect the environment in which that genotype develops. They suggest that the passive, evocative and active gene environment interactions described by Plomin, Defreis and Loehlin (1977) can be viewed with a developmental perspective. Though they make the point that environmental experiences are not necessarily driven by an individual's genotype in extreme circumstances such as deprivation, it might be useful to examine the theory with HSS in mind.

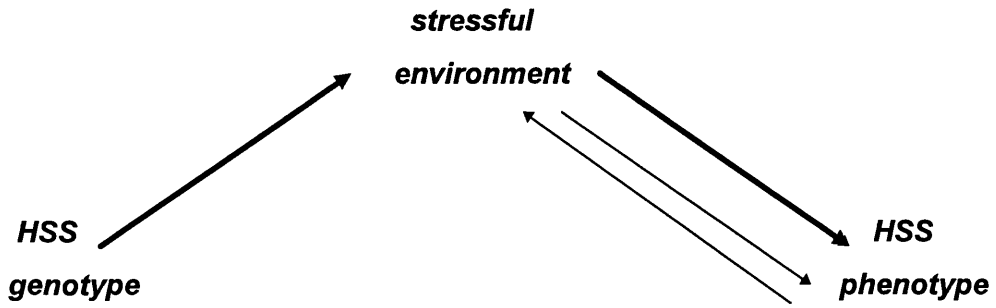
In section 4.5.2.1, we touched on the passive gene environment interaction, suggesting that the cognitive ability of parents influences the type of environment that they provide for their children. The evocative gene environment interaction may be a useful framework in which to consider another aspect of HSS family interactions. We speculated above that the HSS phenotype is expressed to a degree in at least some parents of HSS affected children. Further we have suggested that

the HSS condition might be recessive and therefore both parents must be at least heterozygous for a genetic anomaly. The carrier state might result in a high degree of 'stress reactivity' in parents of HSS affected children. Alternatively, leaving the possibility of parents having the HSS genotype to one side, Bugental, Blue and Cruzcosa (1989) described physically abusive parents as having greater stress reactivity and negative affect than care-givers with no history of abuse, in stressful parent-child interactions. As we have evidence that children with HSS often experience abusive parenting, this trait may apply to the HSS affected families. Whether we take the view that the care-givers of children with HSS are stress reactive due to their HSS genotype, or their environment, or due to a normally distributed population characteristic, or a combination of all these factors, it is clearly possible that they show elevated stress reactivity.

Add to this equation the evidence that children with HSS have behavioural disturbances which may further challenge their care-givers, in addition to those described in 'normal' stressed children. The evocative gene environment interaction suggests that the child's characteristics evoke certain responses from the care-giver. In other words, if the child affected with HSS has feeding problems and sleep cycle disruption in infancy, the highly stress reactive parent(s) might respond negatively. A reactive response from parents will stress the child, perhaps exacerbating their symptoms and so on. Each partner in the dyad may stress one another with increasing severity. The result may be that the child's HSS genotype may in fact be contributing to the stress experienced by that child. Such a gene-environment interaction should not be regarded as 'child blaming'.

The gene-environment interaction theory was developed with quantitative traits in mind, rather than for a discrete syndrome but the concept is still meaningful. The theory that an individual's genotype and consequent phenotype influences their environment to some extent, is an important dimension to consider. It is one that should be viewed in conjunction with the central theme described in the thesis - that the stressful environment results in the HSS phenotype. Figure 5.5.6.1 describes both these influences.

Figure 5.5.6.1: Interactions between HSS phenotype and genotype



In addition to these ideas there are, of course, more purely environmental explanations for extreme intra-familial stress in the HSS affected families, such as modelling, operant conditioning, poor coping strategies, cultural transmission and so on.

5.5.7 Implications

Why should we attempt to identify the core features of HSS, distinguishing them from non-specific stress reactions? First, a constrained definition of HSS will increase the likelihood of establishing linkage. As Rutter notes (1994), false positives are more detrimental to establishing linkage than false negatives. Second, by examining the key features of the syndrome we will be able to make more informed choices of possible candidate genes.

A more immediate benefit is that the information about a syndrome and the phenotype can be used to counsel parents and develop management interventions (Flint 1996) . This is particularly crucial for the families who have a child affected with HSS. As we have demonstrated in the present study, these families tend to be disadvantaged in a number of ways and may need additional support to understand and deal with the behaviours associated with HSS. For example, helping a care-giver to understand that an affected child is hungry as opposed to greedy may be a first step in positive management of HSS. In fact in many ways by labelling sleep

disruption or hyperphagia as part of 'an illness' may go some way to reduce any blame attributed to the affected child by the care-givers.

Perhaps the most crucial implication is that, in contrast to many conditions, adequate intervention and management may also lead to a resolution of the condition's features. In other words, if care-givers can learn to reduce the stress level in the family, the HSS symptoms may improve or resolve. To date in our experience, there is little evidence to suggest that HSS children can recover in the same environment that their symptoms appeared. One attempt at family therapy appeared to be successful initially and so the child was returned home, but the symptoms of HSS reappeared almost immediately. The child was removed from home a second time and consequently showed recovery a second time. Presenting the core features of HSS to care-givers as an illness may improve family dynamics.

We believe that the symptoms of HSS only manifest in stress and have provided data to support this theory. It is also important to note that when an affected child is removed from stress, the core features resolve. Educating care-givers about the aetiology of HSS may result in an improvement of those features by decreasing intra-familial stress, but there remains the problem of the stress, or abuse that caused the HSS features in the first place. 'Curing' a care-giver of emotionally, physically or sexually abusive behaviour towards their child is a separate issue and a daunting task.

If one can demonstrate *without exception* that HSS only manifests in stress and takes the view that recovery within the original environment is impossible, then at the very least, symptoms of HSS may act as a 'flag' indicating stress. The data we have produced to date certainly support this theory, but before HSS is regarded as an invariable marker for stress, more evidence is required. Establishment of an invariable association between HSS and severe stress might be useful in clinical practice. When a child affected with HSS is identified, a closer investigation of their circumstances would be warranted in order to identify the chronic stressor responsible for the HSS symptoms.

5.5.8 Conclusions

This study is the first to describe familial aggregation in HSS and to challenge many assumptions associated with the condition. However, it is limited in many ways as described above, and should not be regarded as the answer to all the questions asked of HSS, but rather as providing data to refine the questions that should be asked. The present findings need to be replicated with larger numbers. Further, investigation into the degree of stress experienced and the way that HSS affected children interpret that stress is required. Objective measures should be used, rather than relying of parental reports. Finally, family studies are limited in describing genetic influences.

Bearing these points in mind, the data we have described tell a plausible story. HSS seems to be a condition that manifests only in severe and chronic stress. The core symptoms of HSS, growth, appetite and sleep disturbance share the same neurophysical pathways as they are all controlled by hypothalamic nuclei (Fix,1995). Such a potential neurological validation provides a theoretical basis for the existence of the condition. As with many of the body's normal physiological stress reactions, the features resolve when the threat in the environment disappears. In sum, the core features of HSS do not seem to be a normative reaction to adversity in childhood and there is evidence of familial aggregation in full siblings. These factors together indicate that HSS may be a stress responsive syndrome, with a neurological substrate, caused by genetic vulnerability.

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Table 4.4.9.3: Behavioural disturbance correlation with age: within groups

	correlation with age		
variable	*HSS*	*PWS*	*stressed*
externalising at school	r = -0.02 p = 0.91	r = -0.10 p = 0.61	r = 0.49 p = 0.02
general externalising	r = 0.11 p = 0.62	r = 0.31 p = 0.10	r = 0.64 p < 0.00
attention/activity problems at school	r = 0.10 p = 0.64	r = -0.03 p = 0.87	r = -0.22 p = 0.30
general attention/activity problems at school	r = -0.13 p = 0.55	r = -0.03 p = 0.86	r = 0.13 p = 0.56
enuresis/encopresis at home	r = 0.33 p = 0.18	r = -0.44 p = 0.02	r = -0.07 p = 0.74
enuresis encopresis at school	r = -0.27 p = 0.20	r = 0.22 p = 0.24	r = 0.25 p = 0.25

Individual item comparisons:

4.4.9.2 sleep disturbance

A number of specific aspects of behaviour were examined using individual items from parent and teacher report. Group means for these items are described in table 4.4.9.4. Sleep disturbance showed a significant group effect (F = 3.56, p = 0.03). A post hoc analysis (Sheffe), taking IQ into account, showed that no two groups were significantly different from one another. Sex effects and interaction effects did not reach significance (F = 0.18, p = 0.68 and F = 0.08, p = 0.92 respectively).

Table 4.4.9.4: Behavioural disturbance individual items: group means

variable	*HSS (n =25) mean (sd)*	*PWS (n= 30) mean (sd)*	*stressed (n = 25) mean (sd)*
self-injurious behaviour	1.40 (1.32)	2.40 (1.13)	1.24 (1.39)
sleep disturbance	1.92 (1.15)	2.23 (1.16)	1.20 (1.22)
poor peer relations (parent report)	1.88 (1.33)	1.27 (1.26)	1.04 (1.21)
poor peer relations (teacher report)	0.52 (0.65)	0.41 (0.69)[4]	0.86 (0.89)[5]

The 'sleep' variable reflects degrees of sleep disturbance. A score of '3', indicates the greatest level of disturbance, describing children who 'roam' at night, playing, destroying items or , in some cases, stealing food . This rating identifies children who have disturbed sleep rhythm, and not simply sleep interruption through nightmares, sleep walking or intrusive thoughts, for example. With this distinction in

[4] data were unavailable for 2 cases
[5] data were unavailable for 3 cases

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Appendix 1

The Hyperphagic Short Stature Syndrome Diagnostic Interview:

The principle of this interview is to obtain behavioural accounts from the primary care-giver across a wide range of functioning. From these descriptions the interviewer will make a judgement rating of abnormality or severity, rather than the parent. The interview includes examples of behaviour for each rating, where possible ICD-10 guidelines have been used to define criteria. A behavioural description should be made by the interviewer on each topic which is sufficiently detailed for tests of inter-rater reliability; that is each rating must be justified by reported behaviour.

The ratings;

0 - A rating of zero indicates normal behaviour (although this does not exclude ANY difficulties in behaviour)

1 - This indicates the behaviour described is either not habitual in nature eg one isolated incident or parental evidence is not strong enough to make the rating of 2. For example the parent may confirm that stealing has happened but be unable to give a specific example .

2 - The behaviour definitely reaches the criteria level of abnormality or severity and there is confirmation the behaviour is typical to some extent. If the informant can recall one single event but indicates this is usual behaviour for the child a rating of 2 (or possibly 3) should be made.

3 - The behaviour definitely reaches criterion level but is of a more severe/abnormal/frequent nature than 2

8 - not applicable (eg where the child is outwith the age range)

9 - not known

History of Behaviour:

To take into account the potentially episodic nature of the syndrome ratings should be made with reference to current behaviour (within 3 mths) but there should also be probing about whether the child has EVER shown this behaviour. Even if a current behaviour reaches criteria, any variation in terms of severity in comparison to the past should be noted. For cases in which reported behaviour seems to have changed significantly, it is important to record changes in family or school circumstances that happened concurrently.

Probes:

Listed below are the 'mandatory probes' which should be used for all types of behaviour. They are written in bold along with mandatory probes specific to the topic. Examples of behaviours can be used to prompt; starting with minor examples. It may be helpful to suggest increasingly severe scenarios to get some idea of where the 'ceiling' of severity lies.

When was the last time it happened ? (use identifiable events where appropriate eg birthdays christmas or use hospital admission as a reference in the shorter term)
Describe what ..... did the last time it happened.
Was that typical of .....?

Expressed Emotion :

As far as possible the probes for Camberwell Family-Interview have been included. These probes are not mandatory but are used at the discretion of the interviewer to elicit attitudes about the child's behaviours and the perceived effect on family circumstances. The Expressed Emotion rating is done subsequently from the tape of the interview. The Expressed Emotion probes are open ended with the intention of inviting the information to reveal his/her attitude towards the index child and his/her behaviour rather than to gather specific information, although this may be helpful too. All EE probes are in italics.

Attribution:

Following each behavioural account there is a direct question concerning attribution. It simply asks the informant why *they* believe the index child showed a particular behaviour. It is important to encourage the informant to focus on the index child's most recent episode rather than a prompt involving that particular behaviour in general. Informants may find it easier to recall a specific recent episode including the context in which it occurred. Recollection of context is important as informants may differ on the degree of importance placed on external as opposed to internal events.

JG May 1994

HSSDI:

NO..... 10

AME.....

K.....

E.....

DRESS.....

.....

.....

ONE NO.....

.....

ADDRESS.....

.....

SPITAL NO.....

NSULTANT.....

TE.....

ld you tell who lives in your house now?
you have any other children who live away from home .
e any of your children been adopted or fostered?

me	dob	sex	address

ACEMENT OF CHILD ON PRESENTATION

CHILD LIVING WITH BOTH NATURAL PARENTS

CHILD LIVING WITH NATURAL MOTHER ONLY WITHOUT FATHER SUBSTITUTE

CHILD LIVING WITH NATURAL MOTHER ONLY WITH FATHER SUBSTITUTE

CHILD LIVING WITH NATURAL FATHER ONLY WITHOUT MOTHER SUBSTITUTE

CHILD LIVING WITH NATURAL FATHER ONLY WITH MOTHER SUBSTITUTE

HILD LIVING WITH OTHER RELATIVE

CHILD LIVING WITH FOSTER PARENTS OR IN AN INSTITUTION

ADOPTION

OTHER

PROBES:

e you ever noticed that X was different to your other children

n was the first time you noticed anything different about X

n did X's difficulties first begin?

s s/he always been this way or did you see gradual changes?

w did you feel about the way s/he behaves?

at do you think makes him/her behave like this?

GGING

you think theses problems have increased the amount you have to nag X?

at sort of things do you have to say?

st families have quarrels, have you and your partner had a tiff/quarrel in the last few months?

at was it about?

e you ever parted over a quarrel even overnight?

you think the amount of quarrelling between you and your partner has increased since X's haviour problems began?

es your partner have to grumble and nag X

at sort of things does s/he say?

at does X do when you have these arguments?

ME BUDGET

w much time would he spend around the house with you on a typical day in the school term?

o else is in the house during these times?
rtner?
s?

at about the school holidays?

RELATIONSHIP

Can you tell me a bit more about how you get along?

Do you find X a friendly child?

Is s/he a friendly person?

Is s/he easy to get along with?

In what ways would you like X to be different?

In what ways does s/he get on your nerves?

Do you feel any differently towards the patient since the behaviours began?

Do you think X has behaved differently towards you?

Do you think the amount of affection X shows you has changed?

In what way?

Are you satisfied with the amount of affection X shows you?

Do you think the amount of affection you have shown X has changed since these problems began?

HOSPITAL ADMISSION

What difference has this hospital admission made to your family?

From your point of view what is the most disturbing aspect of your son/daugters' problems?

HOOL:

ent school:

.....

.....

.....

d teacher.....

ld you have nay objections to us writing to the school for a report on how... is getting on

no
yes

... ever seen a speech therapist:

no
yes

of referral.....

th of referral.....

n for referral.....

e of therapist.....

h authority, or area living when receiving speech

t food stealing (cupboards)

.... take food from the cupboard without asking?
there any foods ... is not allowed eg an unopened packet of biscuits?
s s/he ever take food in this way?
en was the last time it happened ?
cribe what ..... did the last time it happened.
s that typical of .....?
t lengths might ... go to get food - what about at night?

no problem
has been known to steal on limited occasions. No practical measures required to control it. Behaviour stops through verbal reprimand.
vigilance is required to avoid food being taken. Practical measures taken - alarms/locks/sentries. Child shows deviousness in order to get food.
all of 2 plus night roaming to steal food

W:

ER:

---

food stealing(fridge/freezer)

t about the fridge /freezer?
ld ... take ice-cream for example without asking?
en was the last time it happened ?
cribe what ..... did the last time it happened.
s that typical of .....?
t lengths might ... go to get food - what about at night?

no problem
has been known to steal on limited occasions. No practical measures required to control it. Behaviour stopped through verbal reprimand.
vigilance is required to avoid food being taken. Practical measures taken - alarms/locks/sentries. Child shows deviousness in order to get food.
all of above plus night roaming to steal food

W:

ER:

ET: When did it first begin?

RITY: How bad was it?

QUENCY:Did it happen once a week, once a day etc?

IAL CONTEXT: Where did it happen?
was there?

CTIONS: How did everyone present react?
effect did it have on them?

TION: Does it make you feel on edge?
?
re an atmosphere at home?

TIMACY: Do you think s/he could have done any more to control it?

NG: How do you deal with?
effective is that do you think?
re any way to prevent it?

RIBUTION (internal & external factors should be noted):
do you think s/he did that the last time?

.....

.....

stealing from plates

nition: taking food from other family members' plates at least once a week

you all eat together at night?
the children take food from each others' plates. Is that something you allow?
s... do that?.
n was the last time it happened ?
cribe what ..... did the last time it happened.
s that typical of .....?
t can you do to stop it?

no stealing from plates
child will stop when told to do so.
habitual stealing (at least once a week) despite verbal/physical reprimands
habitual stealing (at least once a week) as a result child eats at separate time or in separate room from family.

W:

ER:

---

punishment

: punishments that are age *inappropriate* should be rated as more severe.

t can you do to stop ... taking food
n was the last time you punished him/her?
it make any difference?
ld that be effective with the other children if they took food?

no punishment (despite taking food)
transient and with norms of social acceptability eg
verbal reprimand or withholding privileges/ treats (eg snacks)
punishment is longer in duration eg confinement for 1 hr plus
punishment frankly abusive eg physical punishment with an implement eg belt or emotional abuse
N/A (no stealing)

W:

ER:

prevention:

ere anything you can do to stop ... stealing in the first place?
ere anything practical that can be done?
long have you had to do this?

:

no prevention
warning to stay out of the kitchen/not to steal
lock/alarms or 'sentries' on kitchen but free to be in the rest of the house
child confined to a room
N/A

W:

ER:

---

food hoarding:

en ... does have food, would s/he eat it immediately or might s/he want to hide it away in his room for a time?
you describe what happened the last time you found food hidden away

no hoarding
one occassion
at least two occasions in the last year
once a week or more

W:

ER:

stealing food at school:

the school complained ... eats at school in this way
n was **the last time it happened ?**
ribe **what ..... did the last time it happened.**
that typical of .....?

no food stealing reported
isolated incidents, verbal reprimand stopped behaviour
stealing from lunch boxes/other children's plates; complaints that child makes requests to leave classroom frequently
as above. As a result school have taken practical measures to avoid food stealing eg locking lunch hall

---

overeating

you think that ...eats more than you might expect for a child at that age?
s s/he continue to eat even after you might expect him/her to be full.
n was **the last time it happened ?**
ribe **what ..... did the last time it happened.**
that typical of .....?

none
habitually eats more than other children his/her age
consistently eats so much that child complains of feeling unwell
eats with no apparent sensation of satiety, requiring food restriction as the norm

gorging food

ition: eating a large amount of food in a short time to the point of vomiting

... ever eaten to the point of feeling unwell/ being sick?
n was the last time it happened ?
ribe what ..... did the last time it happened.
that typical of .....?
id you ever have to restrict the amount of food or snacks s/he eats

no gorging
1 or 2 incidents ever eating chocolate/treats to the point of vomiting
gorging to the point of vomiting on more than two occasions but only when given access to large amounts of food on special occasions eg christmas or parties
more than two episodes of gorging to the point of vomiting on everyday food .As a result food may be restricted to avoid gorging

R:

ET: When did it first begin?

RITY: How bad was it?

QUENCY:Did it happen once a week, once a day etc?

IAL CONTEXT: Where did it happen?
was there?

CTIONS: How did everyone present react?
effect did it have on them?

ION: Does it make you feel on edge?
re an atmosphere at home?

TIMACY: Do you think s/he could have done any more to control it?

NG: How do you deal with?
effective is that do you think?
re any way to prevent it?

TRIBUTION (internal & external factors should be noted):
y do you think s/he did that the last time?

.....

.....

: polydipsia

es ..drink excessively?
ve you ever had to refuse.. a drink when he/she asked ?
ve you ever seen .. drink straight from the tap or from the toilet bowl?
hen was the last time it happened ?
scribe what ..... did the last time it happened.
as that typical of .....?

no problem
index child complains drinks more than sibs but not enough to refuse drinks
drinks requests refused child seeks out water/liquid when refused
as 2 plus persistently seeking drinks at night

OW:

ER:

pica

ition: Child over 2 years old, food not culturally sanctioned and has happened at least twice a
for a month or more ? Baltrop (1966) ingestion of one or more inedible substances in the last
weeks?

.. eat food which you wouldn't consider appealing?
d s/he eat frozen food?
about food in dustbins or dog food?
about drinking liquids which you wouldn't normally drink?
was the last time it happened ?
ribe what ..... did the last time it happened.
that typical of .....?

no pica
has eaten frozen/rotten/discarded food twice ever
eats rotten/frozen/discarded food twice in the last six months
as above and consumes non-nutritive substances or toxic substances eg toothpaste or paint at least twice ever

ET: When did it first begin?

ERITY: How bad was it?

QUENCY:Did it happen once a week, once a day etc?

IAL CONTEXT: Where did it happen?
was there?

CTIONS: How did everyone present react?
effect did it have on them?

SION: Does it make you feel on edge?

re an atmosphere at home?

TIMACY: Do you think s/he could have done any more to control it?

NG: How do you deal with?
effective is that do you think?
re any way to prevent it?

RIBUTION (internal & external factors should be noted):
do you think s/he did that the last time?

.....

.....

chewing

... nibble or chew on pencils/pen or toys
about furniture?
t something s/he does unconsciously?
n was the last time it happened ?
ribe what ..... did the last time it happened.
that typical of .....?

no chewing
chews pens/pencils/toys in a distracted manner
chews pens/pencils/toys as a motivated behaviour, with intent
chews items which are not hand-held eg furniture

W:

R:

---

leep

ition: sleep disturbance is non-refreshing sleep causing interference with daily functioning or rmares/terrors or waking earlier, getting to sleep later than is age appropriate at least x3 a , lasting at least a month.

..had difficulty sleeping
you heard him/her get up during the night?
s/he get up very early or go to bed later than you think is acceptable for a child his/ her age?
n was the last time it happened ?
ribe what ..... did the last time it happened.
that typical of .....?

no sleep disturbance or isolated incidents 2- 3 times a year
sleep disturbance but less frequently than criterion
sleep disturbance at least three times a week lasting a month
as 2 including night roaming

W

R

:stealing (non-food)

es ... ever take things that do not belong to him/her from home?
at about school or from shops?
w much were the items worth?
hen was the last time it happened ?
scribe what ..... did the last time it happened.
as that typical of .....?

no stealing or one isolated incident
sporadic stealing (up to 2 times in the last month) of items or money worth less than 50p
stealing items worth £10 or more even on one occasion *or* stealing minor items at least once a week
stealing items worth £10 on more than one occasion

OW:

VER:

Stealing - with whom

.. alone when s/he steals or with other children?
n you tell me who s/he was with the last time s/he stole something?
hen was the last time it happened ?
scribe what ..... did the last time it happened.
as that typical of .....?

child doesn't steal but has been with other children while they have stolen items
only steals when with other children
steals with friends or classmates but index child has stolen alone on at least one occasion
always steals alone
no stealing

OW

VER

t destruction

nition: child must intentionally destroy items rather than accidental breakage

w long **would a new toy last with....**
hat deliberate destruction?
the things that s/he breaks belongings given by or belonging to the same person?
en was **the last time it happened ?**
scribe **what ..... did the last time it happened.**
s that **typical of .....?**

no destruction
isolated incident but clear destruction on one occasion only of own belongings or belonging ibs
persistent destruction of own possessions plus any isolated incident (not more than once as year) of others' possessions
as above , but persistent destruction of others' possessions more than once a month

W:

ER:

SET: When did it first begin?

VERITY: How bad was it?

EQUENCY:Did it happen once a week, once a day etc?

CIAL CONTEXT: Where did it happen?
o was there?

ACTIONS: How did everyone present react?
at effect did it have on them?

SION: Does it make you feel on edge?
w?
here an atmosphere at home?

GITIMACY: Do you think s/he could have done any more to control it?

PING: How do you deal with?
w effective is that do you think?
here any way to prevent it?

RIBUTION (internal & external factors should be noted):
do you think s/he did that the last time?

.....

.....

---

emper tantrums

ition: defiant or oppositional behaviour including aggression. A more severe rating should be where behaviour is developmentally *inappropriate.*

. loose his/her temper easily ?
sort of things make him/her frustrated
s/her worst what does s/he do?
was the last time it happened ?
be what ..... did the last time it happened.
that typical of .....?

no tantrums or less than 3 episodes of shouting/crying in the last year
episodes of shouting /crying/arm waving at least once a month
as 1 plus aggression involving objects eg throwing items (not at a person) or kicking furniture
as 2 plus aggression towards individuals eg sibs/parents

:

:

Enuresis

ition: child must be at least 5 years old.
5- 7 years : at least x 2 a month for 3 months
7 years plus : at least x 1 a month for 3 months

..wet the bed?
t about during the day
ld s/he ever deliberately urinate on the floor or over belongings
n was **the last time it happened ?**
ribe what **..... did the last time it happened.**
that typical of **.....?**

none
nocturnal enuresis ONLY less frequently than criteria
nocturnal enuresis fitting criterion *or* x2 incidents of diurnal enuresis
as above plus child urination in inappropriate places eg over floor or in a public place

W:

ER:

---

ncopresis

ition: Child must be at least 4 years old. behaviour must be shown for six months , at least a month.

.... ever soil her/himself?
this happen when s/he is ill or at other times?
n was **the last time it happened ?**
ribe what **..... did the last time it happened.**
that typical of **.....?**

no soiling or only during episodes of illness
soiling but less frequent than criterion
soiling at least once a month for 6 mths
as 2 but soiling in inappropriate places to cause impact eg smearing of faces

W:

ER:

NSET: When did it first begin?

VERITY: How bad was it?

REQUENCY:Did it happen once a week, once a day etc?

CIAL CONTEXT: Where did it happen?
o was there?

EACTIONS: How did everyone present react?
at effect did it have on them?

NSION: Does it make you feel on edge?
w?
there an atmosphere at home?

EGITIMACY: Do you think s/he could have done any more to control it?

OPING: How do you deal with?
w effective is that do you think?
there any way to prevent it?

TTRIBUTION (internal & external factors should be noted):
y do you think s/he soiled/wet the last time?

.....

u: self-injury

oes... ever pull his/her own hair or bang his/her head
there anything else ... does to hurt him/herself
hen was the last time it happened ?
escribe what ..... did the last time it happened.
as that typical of .....?

none
one isolated incident
head banging/hair pulling-no tissue damage on at least two occasions
injuries causing tissue damage at least two occasions

OW:

VER:

hyperactivity:

nition: must apply across all situations
ast 3 of behaviours for at least 6 mths at a developmentally inappropriate level:

s...
et with hands/feet
e difficulty playing board games
w motor activity which is not appropriate to the situation
e the room in situations where it is not expected
e you had to speak to your doctor about ...
uld this happen at a pry or while watching a film s/he wanted to see?
en was the last time it happened ?
scribe what ..... did the last time it happened.
s that typical of .....?

no problem
less than criterion
criterion
criterion plus professional help employed

W:

ER:

---

attention

inition: must show behaviour across all situations and be present for at least six months and be
elopmentally inappropriate

st behaviours and check them off : at least six of the following behaviours}
able to pay attention to details in tasks or school work
able to sustain attention in a task or in play activities
not listen to what's being said to him/her
es not see a task through to the end (not due to opposition or failure understand
tructions)
s difficulty organising tasks /activities
oid tasks that involve concentration
se thing required for school activities or other tasks
sily distracted by external stimuli eg TV
en forgetful

ave you had to speak to your doctor about ...
ould this happen at a party or while watching a film s/he wanted to see?
hen was the last time it happened ?
scribe what ..... did the last time it happened.
as that typical of .....?

no problems
some problems but below criterion
criterion
criterion and professional help employed

OW:

VER:

: implusivity

finition: must show behaviour across all situations and be present for at least six months and be velopmentally inappropriate

ist behaviours and check them off. at least one of these behaviours}
urt out answers before thinking
tt into a conversation or fail to wait her/his turn
il to wait turn or wait in line
lks excessively without regard to context

ave you had to speak to your doctor about ...
ould this happen at a party or while watching a film s/he wanted to see?
hen was the last time it happened ?
scribe what ..... did the last time it happened.
as that typical of .....?

no problems
some problems but below criterion
criterion
criterion and professional help employed

OW:

VER:

general approach to punishment:

f all the problems we have discussed, which is the most difficult for you to cope with?
hat did you do the last time ... did that [use behaviour given above] ?
hat sort of punishments have you tried in the past?
s anything worked?
ould these punishments work with ...'s brothers/sisters? -
y doesn't that work with ....?

no punishment (despite difficult behaviour)
transient and with norms of social acceptability eg
verbal reprimand or withholding privileges/ treats (eg snacks)
punishment is longer in duration eg confinement for 1 hr plus
punishment frankly abusive eg physical punishment with an implement eg belt or emotional abuse
N/A (no difficult behaviour)

OW:

ER:

: mood (misery)

te: misery must not be confused with sulking because parents refused child's request

scribe ...'s mood in the last week
as s/he quiet and withdrawn?
you know why?
scribe what ..... did the last time it happened.
as that typical of .....?

no withdrawn behaviour
expressed/ demonstrated misery which is transient at least once a week
as above lasting more than an hour, treats / reassurance etc do not help mood at least once a week
mood so severe child unable/unwilling to participate in daily activities

OW:

ER:

u: worries/fears

hat sort of things might ... worry about?
ow do you know this is a worry, does s/he say or do anything which makes you think that?
hen was the last time it happened ?
escribe what ..... did the last time it happened.
as that typical of .....?

no worries/fears
transient worry, easy to reassure
interferes with daily activities (eg reluctant to go to school) but can be persuaded if required
avoidance of topic/activity marked physical distress (tears/panic etc) shown if exposed to situation

OW:

VER:

---

u: friendship

finition: child must be primary school age

oes .. make friends easily?
ould you tell me the name of his/her best friend?
ow old is best friend?
hen was the last time s/he was at a friend's house?
hat about birthday parties?

a best friend and various invitations to other children' homes and to at least 3 birthday parties invitations in the last year
a best friend , only other out of school contact with peers is at birthday parties
a best friend but no other 'out-of school' contact with any other children
as 2 but no best friend named or best friend named is 3 years older/younger

OW:

VER:

ONSET: When did it first begin?

SEVERITY: How bad was it?

FREQUENCY:Did it happen once a week, once a day etc?

SOCIAL CONTEXT: Where did it happen?
Who was there?

REACTIONS: How did everyone present react?
What effect did it have on them?

TENSION: Does it make you feel on edge?
How?
Is there an atmosphere at home?

LEGITIMACY: Do you think s/he could have done any more to control it?

COPING: How do you deal with?
How effective is that do you think?
Is there any way to prevent it?

ATTRIBUTION (internal & external factors should be noted):
Why do you think s/he has lost friends/doesn't have any friends

.....

.....

Thinking about the time you were pregnant with....

Did you feel physically well during your pregnancy?

no physical problems
minor problems eg heartburn; no medical intervention required
relatively minor problems eg blood pressure .Medical intervention required;
major physical problems .

you think your pregnancy with..... was any different in comparison to your other
gnancies
at about the way you felt physically or mentally ?
family circumstances at the time ?

no
yes
no other pregnancies

ify:.....

.....

Maternal postnatal depression

nition: episode must last at least two weeks and must not be due to any organic mental disorder
substance use *plus* symptoms commencing within 6 postnatal weeks for at least two weeks

w did you feel after the birth of.....
teria A; list the symptoms and check off each one}**Did you ..**
lacking in energy,
se interest in activities you enjoyed before,
a depressed mood almost all day lasting persistently for two weeks
teria B :list the symptoms and check off each one}**Did you ..**
se your self-esteem
guilty for no reason
e thoughts of suicide or attempt suicide,
indecisive or have difficulty concentrating
e a change in energy either agitation or retardation
e any sleep disturbance eg unable to switch off at night
erience a change (more or less) in appetite.
you see a doctor?
you get any help eg medication? {get name of medication}
w long were you on the medication?
you feel the same after the birth of all your other children?

no depression or the blues
a total of 4 symptoms, at least 2 from criteria A .
a total of 6 symptoms at least 2 from criterion B
a total of 8 symptoms including all 3 from criteria A

BIRTH

W

other's registered name at time of referral.....

P/ clinic.....

nsultant /GP name.....

edication.....

ngth of time on medication.....

depressed after all pregnancies.....

.....

feeding difficulties

ere there any feeding problems with... when s/he was a baby
hat about sucking and chewing problems?
d anyone describe ... as failing to thrive?
d you get any help with that?
d ... ever have a tube to help her/him feed?

no problem
transient problems with sucking /chewing, no problems with weight gain and no help employed
weight loss/ described as FTT, dietary/eating management required
as 2 plus hospital admission/ tube fed

e of referral.....

other's registered name at time of referral.....

spital/clinic.....

nsultant.....

ration of treatment.....

atment eg dietary management
.....

.....

hich position did you use in the first few months? (show picture)

t what age did s/he begin to sit up like this (show picture).....

---

d his/her head seem 'floppy' during feeding after 6 mths old
d it seem different to your other children at that age?
d you tell your health visitor/GP about it?

no
yes, but no professional help sought
yes, medical help required

---

d you find ... hard to cuddle or feed in the first few months because of very stiff or floppy
mbs?
as that different to your other children at the same age?
d you tell your health visitor/GP about it?

no
yes, but no medical help required
yes, medical help required

E PROBES:

ve you ever noticed that X was different to your other children

hen was the first time you noticed anything different about X

hen did X's difficulties first begin?

s s/he always been this way or did you see gradual changes?

w did you feel about the way s/he behaves?

hat do you think makes him/her behave like this?

AGGING

o you think theses problems have increased the amount you have to nag X?

hat sort of things do you have to say?

ost families have quarrels, have you and your partner had a tiff/quarrel in the last few months?

hat was it about?

ve you ever parted over a quarrel even overnight?

o you think the amount of quarrelling between you and your partner has increased since X's haviour problems began?

es your partner have to grumble and nag X

hat sort of things does s/he say?

hat does X do when you have these arguments?

IME BUDGET

low much time would he spend around the house with you on a typical day in the school term?

Who else is in the house during these times?
artner?
ibs?

hat about the school holidays?

ELATIONSHIP

an you tell me a bit more about how you get along?

o you find X a friendly child?

s/he a friendly person?

s/he easy to get along with?

what ways would you like X to be different?

what ways does s/he get on your nerves?

o you feel any differently towards the patient since the behaviours began?

o you think X has behaved differently towards you?

o you think the amount of affection X shows you has changed?

what way?

e you satisfied with the amount of affection X shows you?

o you think the amount of affection you have shown X has changed since these problems began?

OSPITAL ADMISSION

hat difference has this hospital admission made to your family?

om your point of view what is the most disturbing aspect of your son/daughters' problems?

Mother's height.....

Father's height.....

Mother on medication

no
yes
dk

Specify.....

Father on medication

no
yes
dk

Specify.....

Is your kitchen big enough to eat in?

SIZE OF KITCHEN
1 - NOT USED FOR LIVING IN (LESS THAN 6 FEET WIDE)
2 - USED FOR LIVING IN (LESS THAN 6 FEET WIDE)
3 - NOT USED FOR LIVING IN (6 FEET WIDE OR MORE)
4 - USED FOR LIVING IN (6 FEET WIDE OR MORE)
5 - NO KITCHEN
9 - NOT KNOWN

NUMBER OF ROOMS IN ACCOMMODATION .....

NUMBER OF INDIVIDUALS IN HOUSEHOLD.....

POSSESIONS

0 - NO
1 - YES
2 - MORE THAN ONE

REFRIGERATOR

FREEZER (FRIDGE-FREEZER)

COLOUR TV , Who has the TV?.....

BLACK AND WHITE TV

VAN OR CAR

TELEPHONE

MICROWAVE OVEN.

DISHWASHER.

VIDEORECORDER

ABUSE
0 - NO
1 - LEVEL 1
2 - LEVEL 2
3 - LEVEL 3
4 - HIGH SUSPICION
5 - LOW SUSPICION

0 - NO
1 - YES

PHYSICAL ABUSE.....

SEXUAL ABUSE .....

EMOTIONAL ABUSE .....

NEGLECT.....

DURATION OF ABUSE
0 - NO ABUSE
1 - SINGLE EVENT
2 - LESS THAN ONE YEAR
3 - ONE TO FIVE YEARS
4 - MORE THAN FIVE YEARS

RELATIONSHIP OF PERPETRATOR TO VICTIM
0 - NO ABUSE
1 - BIOLOGICAL PARENT
2 - STEP-PARENT
3 - ADULT SIBLING
4 - CHILD/ADOLESCENT SIBLING
5 - OTHER RELATIVE - ADULT
6 - OTHER RELATIVE - CHILD/ADOLESCENT
7 - ADULT CARE GIVER
8 - CHILD/ADOLESCENT CARE GIVER
9 - ADULT FRIEND/ACQUAINTANCE
10 - CHILD/ADOLESCENT FRIEND/ACQUAINTANCE
11 - ADULT STRANGER
12 - CHILD/ADOLESCENT STRANGER

AT RISK REGISTER
0 - NO
1 - YES

IDENTIFIED GROWTH PROBLEM
0 - NONE
1 - HYPOPITUITARISM
2 - BONE AND CARTILAGE DISORDER
3 - TURNER SYNDROME
4 - FAMILIAL SHORT STATURE
5 - HYPERPHAGIC SHORT STATURE
6 - GROWTH PROBLEM - UNKNOWN ORIGIN

WHO IDENTIFIED (SPECIFY)
1 - MOTHER
2 - GP
3 - PAEDIATRICIAN
4 - HEALTH VISITOR
8 - N/A

Appendix 2

CTLY CONFIDENTIAL

DIFFICULT BEHAVIOUR QUESTIONNAIRE

TO BE COMPLETED BY TEACHERS

E OF CHILD _____ BOY/GIRL

RESS _____ DATE OF BIRTH _____

_____ SCHOOL _____

DTEACHER _____ _____

SS TEACHER _____ FORM _____

E TODAY _____

ow is a list of difficult behaviours that many children show, from time to time. Please give answers according to the way this child has been in the past six hs. Do answer all the questions even if the behaviours described do not apply at all to this child.

would like to know if this child has, so far as you know, ever shown any of the following behaviours in the past six months.. If he/she has shown this viour at all within the past 6 months but is not behaving that way now, tick column 2. If he/she is behaving that way now, tick column 1.

e/she has never, so far as you are aware, shown this behaviour within the past 6 months, tick column 3.

	1 Behaviour happens now	2 Has happened within past 6 months, not now	3 Never	FOR OFFICE USE ONLY
AVIOURS				
Steals food	☐	☐	☐	☐
Lies, makes up stories	☐	☐	☐	☐
Often seems miserable, fed up	☐	☐	☐	☐
Eats rubbish from bins	☐	☐	☐	☐
Soils or loses control of bowels	☐	☐	☐	☐
Wets pants	☐	☐	☐	☐
Drinks excessively	☐	☐	☐	☐
Not much liked by other children	☐	☐	☐	☐
Tends to be on own - rather solitary	☐	☐	☐	☐
Steals money, belongings from teachers or peers	☐	☐	☐	☐
Verbal, physical, or sexual disinhibition	☐	☐	☐	☐
Demands very close attention	☐	☐	☐	☐
Underachieving, compared to others in class	☐	☐	☐	☐
Can't concentrate, can't pay attention for more than a few moments	☐	☐	☐	☐
Rarely says anything about life at home	☐	☐	☐	☐
Seemingly unconcerned about personal hygiene	☐	☐	☐	☐
Tends to be absent from school for unexplained or trivial reasons	☐	☐	☐	☐
Defecates or urinates in public	☐	☐	☐	☐
Eats or drinks things that are inappropriate (eg. pet food, vase-water)	☐	☐	☐	☐

Appendix 3

HOSPITAL FOR SICK CHILDREN

Great Ormond Street

Department of Psychological Medicine

CONFIDENTIAL SCHOOL REPORT

Name: _____ Date of birth: _____

Address: _____ Today's date: _____

_____

Age: _____

1. School details

Name of School: _____ Type of School: _____

Address: _____ Previous School(s): _____

_____ _____

_____

Name of Headteacher: _____ Telephone number: _____

Date of admission: _____

How many classes are there at this age group: _____

Number in class: _____

Are classes streamed: _____

If yes, in which stream is child: _____

Is child receiving or has he/she received any extra help in school, eg, in a remedial group:

If yes, please give brief details:

_____

_____

_____

Attendance: Very poor Poor Good Very good Excellent

If poor or very poor, please give some reasons given by parents:

_____

_____

Attainment and Ability

timated intelligence:	Well above average		High average
Q approx.	120+		110-120
	Average	Low average	Well below average
Q approx.	90-110	80-90	below 80

ease tick according to child's performance compared to others in the same class

	well above average	above average	average	below average	well below average
eading					
umber work					
ral expression					
raft					
ames					
rt					
Written work generally					
Handwriting					
Music					

Results of standardised tests, with dates, would be welcome:

_____

_____

Special Interests

In school:

Out of school:

Details of specific difficulties or special aptitudes:

3. Personality and Behaviour

If the child definitely shows the behaviour described by the statement place a cross in the box under 'certainly applies'. If the child shows the behaviour but to a lesser degree or less often place a cross in the box under 'applies somewhat'. If, as far as you know, the child does not show the behaviour place a cross in the box under 'doesn't apply'.

Please put ONE cross against EACH statement.

		doesn't apply	applies somewhat	certainly applies	for office use only
1	Very restless, often running about or jumping up and down. Hardly ever still.				
2	Truants at school.				
3	Squirmy, fidgety child.				
4	Often destroys own or others' belongings.				
5	Frequently fights with other children.				
6	Not much liked by other children.				
7	Often worried, worries about many things.				
8	Tends to do things on his own, rather solitary.				
9	Irritable. Is quick to 'fly off the handle'.				
10	Often appears miserable, unhappy, tearful or distressed.				
11	Has twitches, mannerisms or tics of the face or body.				
12	Frequently sucks thumb or finger.				
13	Frequently bites nails or fingers.				
14	Tends to be absent from school for trivial reasons.				
15	Is often disobedient.				
16	Has poor concentration or short attention span.				
17	Tends to be fearful or afraid of new things or new situations.				
18	Fussy or over particular child.				
19	Often tells lies.				
20	Has stolen things on one or more occasions.				
21	Has wet or soiled self at school this year.				
22	Often complains of pains or aches.				
23	Has had tears on arrival at school or has refused to come into the building this year.				
24	Has a stutter or stammer.				
25	Has other speech difficulty.				
26	Bullies other children.				

How well do you know this child? very well ☐ moderately well ☐ not very well ☐

4. General Notes on Attitudes (other than given in section 3)

Towards:

Teachers

Adults other than teachers

Other children

---

5. General Notes on Behaviour (other than already given)

In school:

Out of school:

Parents

Please give notes on parental interest shown in work and or behaviour of child

---

Siblings

If the child has had brothers or sisters at your school please give whatever information you think relevant

---

Previous schools, departments or classes

Please give any relevant information available from any of the above

---

9. General notes on anything not covered above:

Signature: .....

Position held in school: .....

Date: .....

Appendix 4

CHILD HEALTH HISTORY

These questions cover health of you and your child from the time you were pregnant.

The questions only apply to .....

Fill in all the questions if you can.

If you want to add any extra information, we would find that very helpful.

All the information is strictly confidental

ID.....

date.....

Please tick the appropriate box

	YES	NO
Was your child born in hospital?		
Were there any concerns about the speed of delivery?		
Was it a forceps delivery?		
Was it a caesarean delivery?		
Did your baby come out head first?		
Were there any other complications?		
Did your baby breathe straight away?		
Was your baby taken to a 'special care baby unit' ?		
Did your baby have jaundice after birth?		
Were you discharged from hospital before your baby?		
Was your baby breast fed?		
Were ALL your babies breast fed?		

Please tick the appropriate box.

	YES	NO
Was your child a planned pregnancy?		
Did you think about a termination during the pregancy?		
Did you consider adoption ?		
Did you fill out a kick chart during the pregancy ?		
Did you smoke during the pregancy ?		
Did you drink during the pregnancy?		

Please answer these questions as fully as possible. Don't worry if you can't remember exactly, approximate answers are helpful too.

	write here
How many weeks pregnant were you when you first found out ?	
How many weeks had you been pregnant when your child was born?	
How long was your baby at birth?	
How much did your baby weigh at birth ?	
What size was your baby's head ?	
How many times have you been pregnant altogether?.	
How many pregnancies survived birth?	
How many terminations have you had?	
How many miscarrages have you had?	
At what age approximately did your child first smile?	
At what age approximately did your child first sit up without any support?	
At what age approximately did your child first walk without help?	
At what age did your child say the first words like 'mummy' or 'daddy'?	
At what age did your child first say short sentences ?	
Did these events happen about the same time with your other children?	

Please tick the appropriate box

	YES	NO
Did your baby suffer from nappy rash in the first two years ?		
Did s/he have gastroenteritis in the first two years ?		
Did your child vomit frequently in the first two years ?		
Did you child have diarrhoea frequently in the first two years ?		
Did your child have any convulsions / fits in the first two years?		
These questions below concern your child's health NOW		
	YES	NO
Does your child suffer headaches ?		
Does your child complain of stomach ache or vomit frequently?		
Does your child have asthma attacks or wheezing ?		
Has s/he ever had brain waves recorded?		
Has your child had dental treatment for teeth overcrowding ?		
Does your child tend to pick at sores or spots?		

What were the weights of your other children, at birth?	
name:	weight:
name:	weight:
name:	weight:
name:	weight:
name:	weight:

Appendix 5

SIB Checklist

I.D Number:

Name :

D.O.B.

SIB CHECK LIST	
short stature	
normal weight	
> 2years old	
HIGH DISCRIMINATION p< 0.001	
eats too much	
gorges and vomits	
steals food at home	
steals food at school	
hoards food	
drinks excessively	
pica	
eats discarded food or from dustbins	
wakes at night and searches for food	
urinates on floor/furniture	
steals (non-food) items	
wakes frequently	

MID DISCRIMINATION ($p < 0.01$ to < 0.05)	
wets pants/ bed	
urinates over belongings	
fidgety	
cannot settle for more than a few mins	
destroys own/ others property	
tells lies	
cannot be trusted	
difficulty making friends at school	
no best friend (parent report)	
not popular at school	
solitary	
overfriendly with stangers	

Appendix 6

Institute of Child Health, London WC1N 1EH
(tel: 071-831 0975)

INFORMATION ON THE STUDY

Some children who have a growth problem for which no obvious physical cause can be found may have inherited a gene which contributed to their short stature. A gene is like a code, which we inherit from our parents, which contains the blueprint for the way we develop physically. We are doing an investigation into the possibility that this gene, which might have been inherited from either or both parents, only leads to slow growth in certain special circumstances. Even if only one child in your family is not growing properly, it is possible that a brother or sister could potentially be affected too. We have come across many families where at least two of the children have a similar growth problem.

So that we can better understand the origins of this unusual cause for short stature we would like to talk to you about the growth of all members of your family, including your own parents. We are especially interested in any eating problems any of you might have had, because they seem to be very common among affected individuals.

As part of our assessment we would also like to take one small sample of blood from everyone in the family. This might help us to discover whether short stature is caused by an inherited condition, and whether other members of the family have the same condition. We can arrange to meet at a time that suits you. It would also be very helpful if we could contact your child's school for some general information about how your child is getting on.

Many of our physical, and perhaps our psychological features too, are inherited. For example, the colour of our eyes. If something goes wrong with our genes that does not always mean we have a serious disease. The gene we are looking for does not cause any life-threatening illness. Many people may have it all their lives yet never have any growth problems or any other disorder caused by it.

At all times the information you give us about your children and your family will be held in complete confidence and will only be made available to research workers working on this project.

If you have any questions about the study please do not hesitate to ring us on the number at the top of the page. If you should encounter any problems with this project or the way it has been conducted then please discuss them with the researcher first. If the problems are still unresolved then you can contact Martin Elliot, Chairman of the Ethical Commitee at Great Ormond Street Hospital who would try an sort out matters for you.

We hope, by understanding the origins of children's growth problems, we will be able to find better ways of treating them in future.

Appendix 7

A POSSIBLY INHERITED FORM OF SHORT STATURE: A FAMILY STUDY

Institute of Child Health, London WC1N 1EH
(tel: 071-831 0975)

INFORMATION ON THE STUDY

Some children with short stature, for which we can find no physical cause, may have inherited a gene that accounts for their growth problem. We know that some of the children we suspect of having this disorder have major disturbances in their eating behaviour which are in many ways like those we see in the Prader-Willi syndrome. The aim of our investigation is to look at the similarities and differences between children with the Prader-Willi syndrome, and those with this unusual disorder of growth.

As you know, your child has the Prader-Willi syndrome, and we understand quite a bit about the genetic basis of the condition. A gene is like a code, which we inherit from our parents, which contains the blueprint for the way we develop physically. We would like to ask a few questions about the family, about the growth of family members including your own parents and other children in the family, if any. Because the eating problem is such a major part of the behaviour of children with Prader-Willi syndrome we would want to ask about that in particular detail. We would like to chat to you, at time that suits you. Only one visit would usually be necessary

Many parents find that managing the behaviour of boys and girls with this condition presents them with considerable difficulties. Often they have not received any specialist assistance with those difficulties. We are hoping that this investigation will help us to obtain a clearer picture of the nature of the disturbed behaviours shown by affected children. We will then be able to devise better ways of helping parents cope. If you are having problems for which you need advice at the moment we would aim to provide it.

At all times the information you give us about your children and your family will be held in complete confidence and will only be made available to research workers working on the project.

If you have any questions about the study please do not hesitate to ring us on the number at the top of the page. If you should encounter any problems with this project or the way it has been conducted then please discuss them with the researcher first. If the problems are still unresolved then you can contact Martin Elliot, Chairman of the Ethical Committee at Great Ormond Street Hospital who would try and sort out matters for you.

If you decide that you no longer wish to participate in the project that is entirely up to you, you are not obligated once you agree in the first instance.

We hope, by understanding the origins of children's growth problems, we will be able to find better ways of treating them in the future.

Appendix 8

CHILDREN'S BEHAVIOUR: A FAMILY STUDY
Institute of Child Health, London WC1 1EH
(tel 0171--831-0975)

INFORMATION ON THE STUDY

The children we see at Great Ormond Street Hospital show a wide variety of behaviour. We know some children have a physical condition which might influence they way they act but we also need to talk to families to gather information on the different types of behaviour that healthy children show. This will mean we can compare the healthy children with those that are in hospital.

We want to understand a bit more about how families cope with different children's behaviour. In order to do this we would like to visit you at home or at Great Ormond Street hospital to talk to your family. It would also be very helpful if we could contact your child's school for some general information about how your child is getting on. Usually only one meeting is necessary.

So that we can understand the relationship between behaviour and physical changes in the body better, we also want to do an investigation of children doing exercise. The exercise will bring about normal changes in the body's hormones, and we can measure them in saliva. We would like to ask your child to do a short aerobic exercise lasting five minutes and then to give a sample of saliva, which just means spitting into a tube.

If you have any questions about the study please do not hesitate to ring us on the number at the top of the page. If you should encounter any problems with this project or the way it has been conducted then please discuss them with the researcher first. If the problems are still unresolved then you can contact Martin Elliot, Chairman of the Ethical Committee at Great Ormond Street Hospital who would try and sort out matters for you.

At all times the information you give us about your children and your family will be held in complete confidence and will only be made available to research workers working on the project.

If you decide that you no longer wish to participate in the project that is entirely up to you, you are not obligated once you agree in the first instance.

We would offer each family who would like to meet with us, a cash sum of fifty pounds.

Appendix 9

Child's Information Sheet

This is to help you understand a little bit more about why I am here today. You can ask any questions about anything you are not sure about.

There are lots of different reasons why some children grow more slowly than others and we want to find out more about these reasons. It doesn't mean there is anything wrong with you because you are a bit smaller than other children your age but it is a good idea to check just in case. This is why you will be going into hospital soon.

In the same way that you have brown eyes like Mummy (or appropriate example for the child) some things run in families we want to know a bit more about what kind of differences run in families which is why we want to chat to all your family today

I want to ask your mummy (mum) a few questions about your brother(s) and sister(s) to see how you all get on at home and school. I will be doing this with lots of other children like you who are coming into hospital soon.

As part of the check-up I talked about, the doctor would like to take a tea-spoonful of blood. Special cream is rubbed on your arm and this will your arm numb for a little while so that it shouldn't hurt at all. It will be very quick. Mummy, Daddy and X ,Y, and Z will be doing this too.

Appendix 10

To identify which cell is significantly different from one another in a chi square larger than 2x2, the following formula was used on the advice of Angie Wade (Biostatistics Unit, Institute of Child Health.

1. For each cell the total row value is divided by the number in the total population

2. This value is multiplied by the total column value to get X

3. X minus the cell value, is squared then divided by X

4. These values, calculated for each cell, totalled will be equal to the final chi square value.

By examining each row's (or in other words, each group's) contribution to the final value it is possible to identify which of the groups is significantly different from the others.

As a additional check the adjusted standardised residuals for each cell were examined. These values were calculated using SPSS (Statistical Package for Social Sciences) as recommended by Everitt (1992)

Appendix 11

The following article appeared in 'Woman's Own' 8th May 1995 and 'Bella' 26th April 1995

Researchers want to hear from parents of children aged between 5 and 14 with Prader-Willi syndrome - a rare disorder which makes them want to eat all the time. The team are trying to find out how families cope with their child's appetite and other behavioural problems. Families will go through a single interview, either in their own home or at Great Ormond Street Hospital in London (travel expenses refunded). Interested parents should contact Jane Gilmour at The Institute of Child Health, 30 Guilford Street, London WC1 1EH (0171831097).