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Growing up with a Chronic Disease

A Survey of Children with PKU in Sweden

BY

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ABSTRACT

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Phenylketonuria (PKU) is an inborn, metabolic disease affecting the enzyme phenylalanine hydroxylase, which converts phenylalanine to tyrosine. Since 1965, all Swedish patients are treated with a diet from the neonatal period, while patients without treatment become severely mentally retarded. This thesis presents a recent survey of intelligence, adjustment, and coping among Swedish patients with PKU aged 8-19 years. In Study I the patients' blood phenylalanine level was in accordance with treatment norms and they were normal in terms of intelligence and adjustment. The next study was a comparison of adjustment between patients with PKU, patients with neurobehavioral disorders, and patients with obesity. A reference group with matched non-clinical children was included. In this comparison, patients with PKU did not differ from the healthy children. Patients with neurobehavioral disorders were the least adjusted, and patients with obesity differed from the reference group and from patients with PKU in some respects, indicating less work capacity and internalising problems. Study II was undertaken for methodological reasons and showed that the measure of adjustment was reliable and valid. Study III was an investigation of psychological mechanisms associated with adherence to the dietetic therapy in PKU. The results showed that parents' problem-focused coping was the main factor behind good adherence. A marked transition to self-care was recommended to enhance the patients' motivation to continue with the diet into adulthood. This thesis concludes that the good outcome among the Swedish patients is due to general improvement of the treatment, but a contributing factor can be the high and fairly equal standards of living in the Swedish society.

Key words: Adjustment, chronic disease, coping, intelligence, phenylketonuria.

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To my daughters,
Sara, Therese and Madeleine
for love and patience
during these years

There is no difficulty in holding current views, and we are all clever in thinking the fashionable thoughts. But to create a new idea, and foresee the development before the time is ripe, that is insight. To see further than the obvious, and to put things into a wider context, is insight.

Asbjörn Fölling, described by his son

LIST OF PAPERS

The present doctoral thesis begins with an introduction about PKU. Then follows a description of the methodology used in the empirical studies*. The studies will be referred to in the text by their Roman numerals:

I Lundstedt, G., Johansson, A., Melin, L., Alm, J. (2001). Adjustment and Intelligence among Children with PKU in Sweden. *Acta Paediatrica, 90*, 1147-1152.

II Lundstedt, G., Melin, L., Alm, J. Adjustment among Patients with PKU, compared with Patients with Neurobehavioral Syndromes and Patients with Obesity. *Submitted*

III Lundstedt, G., Stattin, H., Melin, L., Alm, J. Prerequisites for Diet Continuation in Adolescent Patients with PKU. *Submitted*

CONTENTS

ABBREVIATIONS

ADHD	Attention-deficit Hyperactivity Disorder
AOB	Appraisal of burden
CBCL	Child Behaviour Checklist
DNA	Deoxyribonucleic acid
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, 4th Ed.
EEG	Electroencephalography
HPA	Hyperphenylalaninaemia
IQ	Intelligence quotient
Phe	Phenylalanine
PAH	Phenylalanine hydroxylase
PFC	Problem-focused coping
PKU	Phenylketonuria
SSS	Support-seeking strategies
WISC	Wechsler Intelligence Scale for Children

Introduction

During the last 35 years when newborn screening on PKU has been practised in Sweden, all but one patient has been diagnosed and treated from an early age. Thus, the sensitivity in the screening method is high, and the method for taking blood tests has been improved to minimise the harm done to the child. Nowadays the blood test is performed on the child's hand. The number of patients subjected to treatment is about 180 in our country. By a rough estimate there should be about the same amount of individuals with PKU born before 1965 who are untreated. We do not know much about them. The patients who get treatment, on the contrary, are well known by the doctors, dieticians, and psychologists at the metabolic units.

In clinical psychological practice, you see patients when they have problems, and probably you are biased when it comes to judgement about the patients' situation in general. As a researcher, you need an unbiased starting point, considering the possibility that circumstances can be quite different from what is seen in the clinical setting.

The present work has two aims. The first is to give a non-biased description of the treatment outcome among children and youths with PKU in Sweden. The second aim is to guide clinical psychological work and research on PKU in Sweden.

PKU – an Inborn Error of Metabolism

Prevalence and diagnose of PKU

PKU is an inborn metabolic disease, known since 1934. It was discovered by the Norwegian physician Asbjörn Fölling and is sometimes called "Föllings disease". A mother with two severely retarded children came to see doctor Fölling. The girl was six and a half years old but could not say more than a few words. Her movements were spastic and out of control. The boy was four years old, and he could neither walk nor speak. He could not eat by himself and he had no bladder and sphincter control. The children were surrounded by a special smell. This made doctor Fölling, who was interested in biochemistry; suspect some kind of metabolic disorder. He started an

investigation, which revealed accumulation of Phe in the children's blood and a related substance in their urine. The condition is due to a missing enzyme that metabolises the amino acid Phe, which is required for normal development. High levels of Phe have toxic effects on the nervous system with consequences for cell density and organisation; lower dendrite ramification, fewer synapses as well as disturbed myelination. The disease is autosomally, recessively inherited and in a psychological sense, a reminder of human imperfection.

Treatment has been available for about 50 years, but it has to be preventive and children need to be diagnosed before any symptoms are apparent. Thus, successful treatment presupposes new-born screening, and a screening method was available first in 1963-1964 (Guthrie, 1996; Guthrie & Susi, 1963).

Forty states in Europe and the USA now require that infants be tested. PKU has its highest prevalence in Ireland where it occurs approximately in one out of 4000 births. The disease is detected easily through a blood test, the so-called Guthrie test, which should be performed during the first week of life. Since 1965, all children in Sweden are tested, and in our country there is an incidence of about one case in 30.000 new-borns (Alm, 1981). Later, milder forms of the disease were included, resulting in one case in 20.000 new-borns (Svensson, von Döbeln, Eisensmith, Hagenfeldt, & Woo, 1993).

Effects on brain development, intelligence, and behaviour

Non-treated persons develop deviant body constitution with broad shoulders, a leaning posture and spastic movements. They get hypopigmentation, have a predisposition for eczema, and are recognised by their special odour. Deviant EEG and seizures may occur (Pietz et al., 1993). They are mentally retarded with an IQ of around 50, but sometimes as low as around 20. Other symptoms are irritability, hyperactivity, impulsivity, and destructive outbursts. The lower the IQ, the more severe is the behaviour disorder.

The mechanisms of the brain damage in PKU are still unknown, although several factors have been postulated; defect in myelin synthesis, increase in myelin turnover,

deficiency of neuronal amino acids, impairment of neuronal protein synthesis, and abnormal metabolism of neurotransmitter amines. The immature nervous system is particularly vulnerable to high Phe levels. However, recent research indicates that Phe level in blood is not the only indicator of the risk for brain damage in PKU. There are some cases of individuals with high Phe levels in the blood who exhibit lower brain levels of Phe and are unaffected (Koch, Moats, Guttler, Guldberg, & Nelson, 2000; Leuzzi et al., 2000). The exact critical level for Phe passing through the blood-brain barrier is not known, and there can be individual differences in permeability, with different effects on brain functioning (Möller, Ullrich, & Weglage, 2000).

Issues in the dietetic therapy

The treatment in PKU consists of dietetic therapy and supplementation of amino acids reduced from Phe. Compliance with the diet is measured by level of Phe in the blood (Rupp & Burgard, 1995). Non-treated patients may have Phe levels exceeding 1200 μmol/L. With treatment, the levels decrease to 200-500 μmol/L. This is considered safe with regard to brain development (Weglage et al., 1996) although it is 4-6 times higher than in healthy individuals. In a well-regulated diet, the treated children constantly have a higher level of Phe in the blood plasma.

Whether or not to continue with breastfeeding may be important. When serum-Phe is above 1200 μmol/L in the new-born child, breast-milk is postponed for 1-3 days. The child is allowed a free intake of a nutritionally complete protein substitute without Phe. When serum- Phe is reduced approximately 40-50% from initial value, a set volume of Phe-free formula starts every feed and the mother is then allowed to breastfeed without restrictions afterwards. A Norwegian study (Motzfeldt, Lilje, & Nylander, 1999) showed that infants maintain serum-Phe within the range of 120-400 μmol/L with this method.

PKU patients on a strict diet have homeostatic and lipid profiles comparable with vegetarians (Schulpis et al., 1996), but problems with dietary compliance in adolescents and young adults are known (Antisdel & Chrisler, 2000). The complexity

of the diet may cause rejection and dietary monotony and this can lead to a combination of marginal nutrient intake and high Phe levels (Schulz & Bremer, 1995; Vaz-Osorio, Vilarinho, Carmona, & Almeida, 1993). It is not adequate to reduce the intake of natural protein only (Duran, Rohr, Slonim, Guttler, & Levy, 1999). Reduction in protein synthesis upsets homeostasis; the result is a net catabolism with release of Phe and a further increase in the body pool of free Phe. Intake of the Phe-free amino-acid mixture leads to improved protein synthesis, thereby enhancing incorporation of Phe.

From a psychological point of view, treatment of PKU implies extensive care in the feeding situation, and is not restricted to medication. Compliance with the diet is probably influenced by many different factors, e.g. if the parents are devoted to following the diet and can manage the nutritional task efficiently.

Severity of disease

A large phenotypic heterogeneity is observed in PKU. In view of this, numerous centres have begun DNA studies on the PAH gene, in an attempt to find a genotype/phenotype correlation (Guttler & Guldberg, 1996; Svensson et al., 1993). Severity of disease is divided into two classes: a severe genotype where both mutations totally abolish the PAH enzyme activity, and a mild genotype where at least one mutation results in some residual activity (PAHdb).

To date, well over 400 different mutations have been identified in various populations, but no clear correlation has been found (Burgard, Rupp et al., 1996). There is an association between genotype (predicted residual activity in the enzyme) and Phe tolerance, measured in the blood. The correlation between genotype or Phe tolerance and measures of intellectual development is more ambiguous. In a study on non-treated and mentally retarded adults, some of the patients' siblings were found to have exactly the same genotype and serum Phe level as the affected patients, but were in some cases intellectually normal (Ramus, Forrest, Pitt, Saleeba, & Cotton, 1993). In treated patients, it has not been possible to tell whether severity of disease or serum Phe level has the greatest impact on intelligence (Burgard, Schmidt et al., 1996;

Cechák, Hejcmanová, & Rupp, 1996). However, if the diet is relaxed at the age of 8 years, genotype might be useful in predicting the likelihood of intellectual change, indicating that Phe above a critical level in most cases exerts an influence on intelligence and neurology (Greeves, Pattersson, Carson, Thom, Wolfenden et al., 2000).

Dietary recommendations

Recommendations on the dietetic therapy vary between different centres, depend on the patients' age and state (e.g. pregnancy), and have changed over the years. A recent study suggests no dietary restrictions for those who have a mild form of PKU and Phe levels up to 600 μmol/L on a free diet (Weglage et al., 2001), which is slightly more liberal than the dietary recommendations now followed in Sweden. Since many years, the recommendations in Europe, with few exceptions, e.g. France (Rey, F., Abadie, Plainguet, & Rey, J., 1996), have been to keep the diet at least during the first ten years of life (Griffiths, Paterson, & Harvie, 1995).

In the USA, the same policy has been allowed, although management guidelines have up to about ten years ago been less stringent than in most of the European countries (Azen, Koch, Friedman, Wenz, & Fischler, 1996; Legido, Tonyes, Carter, Schoemaker, Di George et al., 1993; Seashore, Wappner, Cho, & de la Cruz, 1999; Wappner, Cho, Kronmal, Schuett, & Seashore, 1999).

Nowadays a lifelong diet is recommended in Sweden and in many other countries (Cerone, Schiaffino, Di Stefano, & Veneselli, 1999; Fisch, Matalon, Weisberg, & Michals, 1997; Levy, & Waisbren, 1994; Burgard et al., 1999). High levels of Phe are toxic to the nervous system, although the effects may be less detrimental at a higher age and possibly reversible (Cleary et al., 1994; Griffiths, Tarrini, & Robinson, 1997).

Individuals not treated from infancy can still benefit from diet in adulthood. When given dietary treatment, their behaviour improved in general (Brown, & Guest, 1999; Pavone, Meli, Nigro, & Lisi, 1993; Yannicelli, & Ryan, 1995). Although they were still intellectually handicapped, the ability to use their limited capacity was

improved, indicating that the diet promoted executive functions encompassing goal-directed behaviour and problem solving.

Studies on treatment outcome

International research has concentrated on four aspects, when studying the outcome of treatment for PKU. Those are the severity of the disease, at which age the treatment started, quality of dietary control, and the age at loss of dietary control. Discontinuity in early treatment causes a reduction in IQ proportional to the length of treatment interruption (Smith, Beasley, & Ades, 1990). The earlier the break, the more severe are the consequences. Treatment errors during the first two years of life cause mental retardation not possible to repair (Marholin et al., 1978). If treatment of the new-born child is delayed two or three months, it gives rise to a reduction in IQ at the age of six (Cabalaska, Nowaczewska, Sendecka, & Zorska, 1996). Zeman et al. (1996) showed a significant negative correlation between IQ of adolescents and the average level of blood Phe in the first five years of life, but this correlation was less significant later and was not present after the age of 14 years.

In summary, even in early and continuously treated patients there seems to be a slight decrease in the intellectual outcome (Azen et al., 1996; Burgard et al., 1996a). All children with PKU were in the normal range of IQ, but they reached lower levels than their siblings and parents (Scheibenreiter et al., 1996).

Higher-order mental functions

A review of neuropsychological functioning in treated PKU points to some affected areas, such as abstract reasoning, executive functioning, reaction time, and speed of mental processing (Burgard et al., 1999; Schmidt, Burgard, & Rupp, 1994; Schmidt, Burgard, & Rupp, 1996; Stemerdink et al., 1994; Waisbren, Brown, de Sonneville, & Levy, 1994). Elementary forms of information processing are not deficient among early and continuously treated patients. The focus should be on higher-order cognitive processes, e.g. sustained attention (Schmidt et al., 1994). This

can be due to the fact that the right hemisphere and the frontal lobes are more susceptible to lack of dopamine, which might be an effect of a reduced level of tyrosine (Paans et al., 1996; Welsh, 1996). Dopamine heightens attention to external events (Wickelgren, 1997). This was demonstrated in an experimental study of vision-related potentials, which showed subtle differences between children with PKU and healthy children (Henderson, McCulloch, Herbert, Robinson, & Taylor, 2000).

Executive functions include sustained attention, planning, response inhibition, and flexibility as necessary parts in the overall problem solving and goal-directed processes constituting intelligent behaviour. These capacities are signs of integrative mechanisms in the brain, mediated by the frontal lobes. In patients with obvious damages in the frontal lobes, we usually see less efficiency in the executive functions. Restlessness, irritability, and impulsiveness are some characteristics.

School problems among patients with PKU

Deficiencies in the frontal lobes are also related to behaviour problems and can explain the presence of more hyperactivity and impulsiveness among children with PKU (Smith, Beasley, Wolff, & Ades, 1988). Later studies have shown signs of negative task orientation and extraversion, but far less than children who meet the ADHD criteria (Kalverboer et al., 1994). A longitudinal study from Hungary showed normal development of physical growth and IQ in early and continuously treated patients (Schuler et al., 1996). However, the same study reported that from a sample of 107 patients, normal school was attended by 82% while 18% were in need of special elementary education.

Problems with academic achievement were also reported in some other studies (e.g. Chang, Gray, & O'Brien, 2000; Stemerdink, 1996; Weglage, Funders, Wilken, Schubert, & Ullrich, 1993). The children seemed to be affected in some situations where the demands on concentration, problem solving and planning were pronounced, and teachers judged patients with PKU more negatively as for their attitude to school. Stemerdink (1996) pointed out gender differences. Boys seemed to be more

susceptible to lack of dopamine, as they showed lower results on tests measuring attention span and endurance.

Psychological measures of treatment outcome

The assessment of intelligence has been of great concern in the evaluation of treatment for PKU. WISC is the most commonly used test for measuring intelligence, giving highly reliable data on the child's verbal capacity and on logical and abstract reasoning. It has obvious advantages because it is standardised and international. It does, however, have limitations. WISC is primarily a test measuring basic intellectual functioning, and unless the latest and extended version is used, it does not test higher order functions (Kaufman, 1994). Other tests measuring executive functions are the Stroop test, which is a test of response inhibition, and Letter Cancellation, a test of sustained attention and Design Fluency for measuring creativity (Griffiths et al., 1997a). Although these different tests provide important information on the child's capacity, they do not give information on functional and global aspects, which are important when we consider higher order functions. Higher order functions are not distinct from basic functions. They are the result of organisation, encompassing attention span, memory, problem solving, mood, and flexibility, directed by perceived motives and goals.

To assess intelligence one should consider how much learning takes place, but also the kinds of learning. Both amount and kind are affected by motivation. It is obvious that the environment influences the way intelligence is expressed, as one can have a high motivational level in one direction but low levels in others. Higher order mental functions are derived from both inner biological conditions and environmental sources (Kalat, 1995).

Hence, additional practical tests may be of value to understand intelligence fully. People do not think or behave intelligently in a vacuum, nor can society set standards for what constitutes intelligence without reference to the functions people perform in different situations (Gardner, 1993; Sternberg, 1990). The development of an individual from childhood to adulthood occurs in a process, which is characterised by

continuous interaction between the individual and his/her environment. This process is conceived and studied as a process of adjustment (Magnusson, Dunér, & Zetterblom, 1975; Magnusson & Stattin, 1996). Thus, it is important to investigate children's ability to adjust and be constructive in their own special environment. For these reasons, not only WISC but also new means to assess adjustment are devised in *Study I and II.*

A Measurement of Adjustment

Construction of an assessment scale

Adjustment difficulties among chronically ill children are a consequence of age-delayed behaviours, diminished functioning and behaviours that are normal responses to abnormal situations, and difficulties can show up in many different ways. A child exists in relationships with others and adjustment reflects those different relationships. This is what happens in the formation of the attachment bond between the child and its parents and then continues to happen in different settings (Bretherton & Waters, 1985; Farrell Erickson, Sroufe, & Egeland, 1985; Main, Kaplan, & Cassidy, 1985; Meltzoff, 1985; Murray & Trevarthen, 1985; Stern, Hofer, Haft, & Dore, 1985).

Two areas of importance for a child's adjustment are work capacity and social competences (Cavell, 1990; Harter, 1982; Rydell, Hagekull, & Bohlin, 1997). They influence how the child perceives him- or herself, and how parents and teachers perceive the child. Adjustment can be investigated from this positive point of view and give a measure of strengths and abilities.

More common however is to look for problems, which can be disturbing in the normal developmental process (Sroufe & Rutter, 1984). One commonly used method in assessing adjustment problems is the Child Behaviour Checklist, CBCL (Achenbach & Edelbrock, 1979). This inventory of behavioural problems indicates two different dimensions of externalising and internalising problems, which have high discriminative validity among normal and clinical samples.

Recent research on adjustment focuses on both strengths and weaknesses and on their interrelationships (Smedje, Broman, Hetta, & von Knorring, 1999; Wingenfeld, Lachar, Gruber, & Kline, 1998). In the present thesis, the questionnaires consisted of items on work capacity, social competence, externalising behaviour, and internalising problems. The questionnaires were designed to be a screening instrument to use among children with different medical diagnoses, not only PKU. A brief review of global psychosocial variables and the use of multi-informant questionnaires may be the best tools with which to identify children with chronic illness at risk for emotional and behavioural problems (Bird et al., 1993; Harris, Canning, & Kelleher, 1996; Howells Wrobel & Lachar, 1998).

Psychometric properties of the questionnaires

The questionnaires consist of 42 items and exist in three forms, one for teachers' ratings, one for parents' ratings, and one for self-ratings. The answers were given on a five-point Likert scale, indicating amount of abilities and problems. A principal components factor analysis with varimax rotation supported a four-factor solution in the three questionnaires; work capacity, social competence, externalising behaviour, and internalising problems (Table 1).

To be able to examine a broad index of problems in the children, a composed measure was calculated by adding the scales work capacity, social competence, and externalising and internalising problems (reverse coding). For homogeneity of the four scales and the composed measure, see Table 2.

Table 2

Homogeneity (Cronbach's alpha) for the four scales and the total scale in the three sources of information

	Teacher's ratings	Parents' ratings	Self-ratings
Work capacity	.94	.90	.87
Social competence	.92	.87	.76
Externalising	.79	.80	.81
Internalising	.87	.89	.82
Total scale	.95	.94	.90

Table 1

Factor model of the three parallel versions of the adjustment questionnaire; teachers' ratings (N=136), parents' ratings (N=274), and self-ratings (N=324). Principal Component Analysis, varimax rotated, explained variance 55%, 48% and 41%, respectively

	Teachers' ratings				Parents' ratings				Self-ratings			
Factor 1 Work capacity												
Easy to concentrate	**.81**	.20	-.17	-.20	.20	**-.60**	-.37	.19	.44	-.08	-.17	**-.49**
Insecure about new tasks*	**.53**	.17	.02	-.44	.19	**-.41**	-.37	.01	-.02	-.13	**-.40**	-.34
Tries his/her best in school	**.68**	.23	-.35	-.15	.05	**-.70**	-.05	.25	.45	-.06	-.10	**-.55**
Persistent if needed	**.76**	.31	-.26	-.01	.21	**-.60**	-.15	.35	.19	-.39	-.02	**-.43**
Interested in new tasks	**.66**	.31	.01	-.40	.29	**-.50**	-.09	-.01	.12	-.26	-.03	**-.63**
Tries difficult tasks	**.61**	.17	.06	-.43	.19	**-.60**	-.09	-.07	-.03	-.21	-.04	**-.73**
Works quickly	**.73**	.17	.03	-.35	.11	**-.68**	-.16	-.02	-.09	-.15	-.12	**-.59**
Difficult to finish tasks*	**.75**	.26	-.10	-.10	.12	**-.60**	-.30	.37	.34	-.15	-.27	**-.40**
Gives up at hard tasks*	**.67**	.27	-.09	.07	.24	**-.51**	-.35	.30	.12	-.13	-.25	**-.59**
Thorough	**.67**	.27	-.10	.07	.20	**-.60**	-.04	.40	.13	-.32	.05	**-.54**
Satisfied with his/her work	.51	.14	-.09	**-.57**	.00	**-.67**	-.26	.06	.39	-.02	-.05	**-.61**
Wants to complete tasks	**.80**	.29	-.05	-.01	.23	**-.71**	-.09	.20	.29	-.27	-.03	**-.64**
Does homework	**.56**	.14	-.18	-.13	.07	**-.59**	-.02	.42	**.54**	.14	-.08	-.49
Factor 2 Social competence												
Comforts peer	.22	**.78**	-.15	-.05	**.68**	-.10	-.16	.06	.21	**-.63**	.15	-.01
Sees how peers' feel	.29	**.73**	-.18	-.09	**.67**	-.08	-.20	.29	-.21	**-.48**	.01	-.20
Notices injustice	.16	**.42**	.22	-.13	**.51**	-.09	.04	.08	-.02	**-.44**	-.01	-.20
Shares/lends belongings	.16	**.72**	-.11	-.21	**.48**	-.18	-.24	-.09	-.06	**-.56**	-.05	-.00
Generous	.23	**.75**	-.27	-.20	**.58**	-.01	-.26	.24	-.10	**-.57**	-.10	-.07
Prevents conflicts	.20	**.71**	.07	-.33	**.68**	-.04	-.12	-.05	.07	**-.67**	.03	-.11
Gives compliments	.07	**.77**	-.12	-.22	**.71**	-.22	-.12	.05	.09	**-.61**	-.05	-.13
Finds solutions to conflicts	.26	**.78**	.05	-.23	**.59**	-.33	-.17	-.01	-.02	**-.44**	-.12	-.14
Can show liking	.23	**.80**	-.28	-.02	**.76**	-.16	-.17	.14	-.02	**-.38**	-.12	-.11
Helpful to peers	.22	**.72**	-.22	-.00	.40	**-.47**	-.15	.13	.23	**-.42**	-.22	-.12

V.g. vänd

Factor 3 Externalising												
Bullies*	.10	.36	**-.54**	.11	.24	-.01	-.28	**.49**	**.53**	-.03	-.16	.06
Has stolen money*	.03	.11	**-.43**	-.13	.19	-.08	-.16	**.63**	**.65**	.01	-.10	-.12
Has shoplifted*	.15	.14	**-.65**	-.13	.01	-.05	-.14	**.65**	**.60**	.17	-.04	-.20
Smokes*	.09	-.17	**-.47**	-.06	-.16	-.14	-.06	**.45**	**.52**	.33	-.09	-.24
Has unapproved friends*	.18	.09	**-.68**	-.11	-.02	-.15	-.19	**.68**	**.62**	-.07	-.04	.03
Destroys things voluntarily*	.06	.19	**-.75**	-.10	.37	-.15	-.37	**.50**	**.70**	-.08	-.02	-.03
Behaves thoughtlessly*	**.53**	.18	-.28	.18	.16	-.17	-.34	**.43**	**.53**	-.04	-.31	-.15
Outbursts of anger*	.33	.17	**-.50**	-.26	.37	-.10	**-.50**	.33	.41	-.08	**-.47**	-.09
Stays out past curfew*	.35	.18	**-.63**	.04	.06	-.14	.13	**.60**	**.59**	-.18	.01	.00
Plays truant from school*	**.36**	-.16	-.17	-.11	-.15	**-.38**	-.05	.30	**.65**	.26	-.07	-.30
Lies to get out of trouble*	.22	.16	**-.52**	-.18	.21	-.10	-.25	**.54**	**.54**	-.06	-.34	-.15
Factor 4 Internalising												
Lonely and sad*	-.01	.22	-.23	**-.77**	.08	-.07	**-.84**	.07	-.01	-.02	**-.77**	.04
Doesn't feel liked*	.11	**.54**	-.16	-.47	.28	-.06	**-.74**	.17	.04	-.10	**-.72**	-.04
Sleeps badly/seems tired*	**.53**	-.00	-.09	-.43	.02	-.18	**-.59**	.17	.24	.08	**-.44**	-.00
Feels unhappy*	.11	.30	-.28	**-.69**	.16	-.13	**-.83**	.10	.13	.02	**-.79**	-.11
Lacks friends*	.05	.45	-.10	**-.57**	.26	-.08	**-.74**	.10	-.06	-.20	**-.63**	.04
Doesn't feel good enough*	.21	-.02	-.18	**-.76**	.02	-.28	**-.64**	.18	.15	-.03	**-.76**	-.14
Weak and powerless*	**.52**	.28	-.06	-.51	.24	-.39	**-.52**	.20	.31	-.03	**-.36**	-.35
Enjoys life	.28	.36	-.12	**-.68**	.21	-.25	**-.63**	.06	.04	-.01	**-.60**	-.20

*Reversed item

The validity of the questionnaires was considered from different points of view. The theoretical domain of developmental psychology concerns many abilities with different value implications and social consequences (Messick, 1995). Items were collected with reference to their functional importance for the individuals' adjustment in school and at leisure time. The four scales were chosen to give a representative picture of both children's and youths' functioning in social, cognitive, and emotional respects.

Coping with Chronic Disease

Coping with PKU

In Sweden, all children with PKU are treated from an early age and dietary control should be kept into adulthood. One important question in contemporary research on PKU is about maintaining the diet for life. As in other chronic conditions, e.g. diabetes, coping strategies are best understood within the context of illness-specific situations (Grey, Lipman, Cameron, & Thurber, 1997; Reid, Dubon, Carey, & Dura, 1994). In *Study I* the association between Phe level and background variables were investigated. In *Study III* the background variables were related to contemporary Phe level, with coping as a potential mediator (Baron & Kenny, 1986; Holmbeck, 1997).

Coping with PKU means drinking the Phe-free amino-acid formula every day, keeping a low protein diet, and taking blood tests regularly. Treatment entails considerable restrictions in the diet, especially for patients with the severe form of the disease, and the psychological adjustment to the disease is viewed as a continuous process over time. This process is active in forming methods of coping, which concerns both appraisal of the disease, inner regulation of feelings, and adaptive behaviour (Aldwin, 1994; Compas, Banez, Malcarne, & Worsham, 1991; Lazarus & Folkman, 1984; Skinner & Edge, 1998). Coping is in essence the ability to find solutions in daily life and it is conceptualised as the normal and healthy way of handling stress.

Coping and mental health

There is considerable overlap between the concepts stress and anxiety. When someone faces an extraordinary situation, there is a risk for breakdown. Thus formulated, the view of psychopathology is that it is a product of stress when coping efforts have failed (Aldwin, 1994). We can consider the three dimensions: focus of attention, sociability, and response level as three measures of coping quality (Zeidner & Endler, 1996).

First and foremost, it is important to pay attention to the disease. Accurate perception of the symptoms has proven to be important for self-care in other chronic conditions, e.g. paediatric asthma (Fritz, McQuaid, Spirito, & Klein, 1996). In PKU there are no obvious symptoms, only a threat against future health. The treatment should be directed by the awareness of the consequences of the PAH deficiency, which presuppose adequate knowledge and confidence in managing the diet.

Second, to increase conceptual clarity it is appropriate to define coping as a positive resource in the personality, enhancing social relationships. Ambiguous coping strategies such as emotion-focused coping and avoidance should be left outside the domain of coping. Defence mechanisms are apparent in different forms of personality disorders and mental disorders. Avoidant strategies were associated with adjustment difficulties and worse metabolic control among adolescents with diabetes (Grey, Cameron, & Thurber, 1991). Withdrawal and inability to establish close relationships are signs of beginning mental illness.

Finally, response level is in many ways dependent on the more basic functions of attention and sociability, and behavioural and cognitive response is a reflection of the quality of the overall coping process. While stress is an inevitable aspect of human life, it is coping that makes the big difference in adjustment outcome (Compas, Malcarne, & Fondacaro, 1988). It is important to make a conceptual distinction between strategies involving defence mechanisms and coping strategies.

Parental coping

Recent studies have established an association between parental characteristics, including parenting style and parents' ways of coping and children's coping (Compas, 1998). Child coping can be understood partly as a mirror of family characteristics, where family resources as well as individual competencies or resiliency of the child can buffer the effects of the child's illness (Hamlett, Pellegrini, & Katz, 1992). This represents a new and important area for research and has guided the design of *Study III*.

For the parents, it is stressful to be informed of the child's disease and aversive life events can disrupt competent parenting (Awiszus & Unger, 1990; Simons, Lorenz, Wu, & Conger, 1993). The message from the hospital that the child is ill raises many questions about the child's state and further development. The way the parents are informed about their child's' diagnosis is important for their coping efforts. Especially the affective component in the parent and doctor communication has shown to be a strong predictor of satisfaction (Quine & Rutter, 1994).

As the stressors in having PKU are related to food and eating, they are an every-day challenge and it can be more or less trying in different situations. If the parents have managed those stressors constructively, the child is supposed to accept the situation and integrate the awareness of the disease. For the child it is not the kind of emotional shock to face the disease as it may be for the parents. It is rather a step-wise maturation of insight and transition of own responsibility.

Considering the dynamic nature of coping with PKU, a longitudinal analysis is important for full comprehension (Berg, Meegan, & Deviney, 1998). Variations in the course of the disease, family strains independent of the disease, and developmental changes in the child all require attention, although this goes beyond the purpose of the present work.

Positive family functioning is associated with improved adherence to treatment, which is associated with good metabolic control. Most research on coping points to the adjustment of the mother particularly (Bronfenbrenner, 1979; Thompson & Gustafson,

1996). Although child coping primarily is associated with maternal coping (Kliewer, Fearnow, & Miller, 1996), it is also important to pay attention to the situation of the mother as dependent on the father's attitude and support. To understand parenting and its influence on child development, attention should be accorded to the marital relationship (Belsky, 1984). With few exceptions, studies have tended to neglect the father in the analysis of coping with chronic disease onset and most studies have neglected the interplay among family members that modifies adjustment (Frank, et al., 1998). In *Study III* the parents' civil status was taken into account.

Child and adolescent coping

Child coping means particularly that the child is receptive to the parents' treatment of the disease. Coping is connected with intelligence since problem solving is the core of intelligent behaviour. Children can differ in temperament and attention capacities such as attention span, attention control, and distractibility. Those capacities are moderately stable in infancy and they are relevant for parents' perception of their child. The interplay between child and parents changes with age and so does the level of demands. In the present investigation, the patients were grouped according to age, and children aged 8-12 years were compared with youths aged 13-19 years.

By adolescence, patients typically take substantial control of their dietary intake, often with little input from parents and more from peers and other external influences. Youths with chronic illness need to adapt to more stresses than do healthy youths and their need for adaptive coping strategies are pronounced (Freitas & Downey, 1998; Olson, Johansen, Powers, Pope, & Klein, 1993; Weglage, Funders, Ullrich, Rupp, & Schmidt, 1996).

The need for life-long treatment

The patients born before 1986, and their parents, have followed the advice to continue with the diet during childhood. The diet is thereafter relaxed, resulting in progressive elevation of Phe levels. As yet, it is uncertain how beneficial it is for

adults with PKU to remain on low Phe diet. Griffiths, Smith, and Harvie (1997) found no cognitive or behavioural effects of HPA in an experimental study. Sixteen well-treated patients aged 10-16 years were given a high Phe supplement in a triple blind crossover study without any change in psychological test data; moreover, patients and parents were unable to guess whether the Phe levels were high or low.

On the other hand, there may be some longer-term effects of coming off the diet. Brain development continues with myelination up to about 30 years of age. Nutritive intake may be crucial in this process. Recent studies have shown that discontinuation of diet in adolescents or adults is associated with white matter changes on MRI scans of the brain (Cleary et al., 1994; Diamond, Prevor, Callender, & Druin, 1997). It is not yet clear if these changes lead to neurological problems. There have been reports of patients who develop abnormalities upon discontinuing the diet and in some cases the abnormalities resolved when diet was resumed (Cerone et al., 1999; Pietz et al., 1997). On the other hand, the vast majority of patients who discontinue the diet do not develop any abnormalities in the short term (Schmidt, Burgard, Pietz, & Rupp, 1996). As yet patients have not been followed for long enough to know if they will have long term problems and it is largely for this reason that diet is now recommended for life.

The risks of treatment must also be taken into account. The worst option is to remain on a restricted diet without supervision or taking adequate supplements, since there is a very real risk of nutritional deficiencies, particularly vitamin $B_{12,}$ resulting in neurological as well as psychiatric disorders (Robinson et al., 2000; Vaz-Osorio et al., 1993). Clearly, the decision about diet continuation in adults needs to be made by the patients once the available evidence has been explained to them. Singh, Kable, Guerrero, Sullivan, and Elsas II (2000) among others, conclude that many adolescent patients are not equipped to make appropriate choices to comply with their diet prescription and maintain their targeted metabolic control. Patients must be followed up even if they discontinue diet, since many patients have grown accustomed to a strange diet and will therefore remain at risk of nutritional deficiencies.

The parental and child coping scales

In order to investigate different psychological mechanisms of importance for compliance with the diet in PKU, two measures of coping were developed. The measures were based on previous research in this area (Ayers, Sandler, & Twohey, 1998; Band & Weisz, 1988; Carver, Scheier, & Weintraub, 1989; Spirito, Stark, Gil, & Tyc, 1995) and were adapted to different kinds of strain experienced by parents and children, and the influence parents might have on child coping (Kliewer et al., 1996; Kortlander, Kendall, & Panichelli-Mindel, 1997; Sandler, Tein, & West, 1994). For the construction of those two coping questionnaires, the PSCQ, (Parental Socialization of Coping Questionnaire; Miller, Kliewer, Hepworth, & Sandler, 1994) and the CCSC, (Children's Coping Strategies Checklist; Ayers, Sandler, West, & Roosa, 1996) have been of considerable use. Since no coping scale applied to PKU was available in the literature, the scales used in *Study III* were developed with help from an experienced dietician. Items were collected with regard to their functional importance for maintaining Phe level within the recommended range.

The parents' coping scale was divided into three parts (Table 3). The first was a retrospective measure of manageability and control during the period when the new-born child was diagnosed and the treatment started. Then followed an evaluation of the contemporary situation. Those two parts measured how different situations were handled by support-seeking and/or problem-focused coping. The last part of the parental coping questionnaire concerned appraisal of burden imposed by the illness, which was supposed to be associated with the parents' coping capacity (Hentinen & Kyngäs, 1998). According to Mailick, Holden, and Walther (1994) it is important to make a conceptual distinction between the burden imposed by the illness and the coping skills used by caretakers. Yet they are related, and can be regarded as different dimensions of the over all coping capacity (Lazarus & Folkman, 1984). Positive cognitive restructuring enhancing emotional balance might contribute to coping with chronic disease. Once dietary control is learned and followed in PKU, the patients have no symptoms and the disease is not associated with pain or physical limitations.

The attitude to the disease - the appraisal of burden - is a question of cognitive and emotional coping with the diet.

Table 3

Parental coping questionnaire, PFC=Problem-focused coping, SSS=Support-seeking strategies

Part I Manageability and control during the child's first years.	
1. When we got the message about the illness:	
-we tried to get informed about PKU	PFC
-we felt support from the hospital	SSS
2. During the child's first year:	
-we tried to learn the nutritive value of different foods	PFC
-we tried to follow the dietician's advice accurately	SSS
3. During the pre-school years:	
-we got help and support from the hospital with the child's diet	SSS
4. Our child's diet has been:	
-easy to learn	PFC
-easy to follow	PFC
Part II Contemporary manageability and control.	
5. When our son/daughter is travelling:	
-we prepare special food	PFC
6. At celebrations and feasts:	
-we let our child eat the same as we do*	PFC
7. When our son/daughter gets sick:	
-we try to satisfy the calorie requirement anyhow	PFC
-we get the information and support we want from the hospital	SSS
8. When our son/daughter takes blood tests:	
-we can ask someone else for help	SSS
9. When the result from the blood test arrives:	
-we don't think about it*	PFC
-we plan the diet with extra care	PFC
10.When our son/daughter is going to the hospital:	
-we get the support we need	SSS
-we learn new things	PFC

* Reversed item

Part III Appraisal of burden imposed by the illness (AOB)

Our child with PKU has increased conflicts in our family*

I often feel sad about my chronically ill child*

I believe that my child with chronic illness will manage in life equally well as a healthy child

It is permissible in our family to express feelings

It is my fault if things go wrong with the child's treatment*

I am afraid of the future*

I demand the same from my chronically ill child as from a healthy child

I have time for my friends and other close people

The child's illness has changed relationships between the parents negatively*

My child's treatment is very difficult*

It is difficult for me to talk about my child's disease*

I often feel helpless in caring for my chronically ill child*

The chronically ill child has decreased connections outside our family*

I have no time for other close relatives, because of the time-consuming treatment*

* Reversed item

The difference between the parents' and the children's coping questionnaire is based on the different meaning and practical consequences the disease has for them. In the child coping questionnaire, the three scales assessed concurrent coping (Table 4).

The answers on both coping questionnaires were to be given on a four point Likert scale (disagree-agree). A principal factor analysis was run although the sample sizes were small; only 46 and 44 subjects respectively. A varimax rotation yielded three scales labelled appraisal of burden (AOB), problem-focused coping (PFC), and support-seeking strategies (SSS) in both parent and child coping questionnaires. The homogeneity of the scales in both questionnaires was considered acceptable. Cronbach's alpha for the parents' scale was AOB=.89, PFC=.83, and SSS=.69, and for the children's scale AOB=.68, PFC=.80, and SSS=.84.

A sum of the parents' and children's' scales was calculated, yielding 30 items in each scale. Cronbach's alpha for parents' total scale was .79 and for children's' total scale was .80. This sum scale was considered a reliable measure of the ability to cope with PKU emotionally, cognitively and at the behavioural level.

Table 4

Child coping questionnaire

AOB=Appraisal of burden, PFC=Problem-focused coping, SSS=Support-seeking strategies

1. When I am at home:	
-I drink amino acids 3-4 times/day	PFC
-my parents prepare my food	SSS
-I prepare wholesome food for myself	PFC
-I eat food I am not supposed to*	PFC
-I often wish not to have PKU*	AOB
2. When we have lunch in school:	
-I drink my amino acids	PFC
-I ask for help to get my food	SSS
-I fetch my food in the kitchen	PFC
-I want to sit alone and eat*	AOB
3. When I am invited to someone:	
-I tell them about my diet	SSS
-I don't eat anything at all*	PFC
-I bring my own food	PFC
-I want my parents to help me get my special food	SSS
-I give up my diet and eat the same as the others*	PFC
4. When someone asks me about my illness:	
-I answer something plain that some food does not suit me	AOB
-I leave them*	AOB
-I start talking about something else*	AOB
-I can show my gratefulness for their consideration	AOB
-I get sad and don't want to talk about it*	AOB
5. When we have an excursion in school and on leisure time:	
-I want help from others to get my food	SSS
-I give up my diet and eat the same as others*	PFC
6. At celebrations and feasts:	
-I eat the same food as others do*	PFC
7. When I am sick:	
-I still try to keep good values	PFC
-I give up my mixture*	PFC

8. When I am taking my blood test:	
-I want my parents to help me	SSS
-I think it is unnecessary and stop it*	PFC
-I know it is important, but I stop it anyhow*	PFC
9. When the result of the blood test arrives:	
-I don't care about it*	PFC
10. When I am in the hospital:	
-I want to learn new things	PFC
-I wish to stay a little longer	SSS

*Reversed item

Empirical studies

Research questions

Most research on PKU has shown a normal outcome among early and continuously treated patients, although slight reductions in IQ and prevalence of adjustment problems have been reported.

The general aim of the present thesis was to evaluate the treatment of the patients with PKU in Sweden. Patients with PKU were compared with two other groups of patients and a non-clinical reference group. Besides, the coping concept was applied to PKU, and psychological aspects of importance for diet continuation from adolescence onward was explored. The thesis addresses the following questions:

- What is the outcome among children with PKU in Sweden in terms of dietary control, IQ and adjustment?
- What about adjustment among patients with PKU compared with patients with neurobehavioral disorders and patients with obesity?
- What is the impact of parental and child coping on dietary compliance?
- What are the effects of specific background variables?

Organisation of the project

The project was carried out in co-operation with the university hospitals where patients with PKU are treated, i.e. Uppsala, Stockholm, Umeå, Gothenburg, Malmö, and Lund. In *Study II* were included patients with neurobehavioral syndromes, treated at the local centre for disabled children in Borlänge and Hedemora, and patients with obesity, treated at Huddinge University Hospital in Stockholm. *Study I and II* comprised a reference group of healthy children. They were recruited from ten schools in urban and rural districts.

The patients and their parents were informed about the investigation, and after that, they received a mailed questionnaire. Parents to patients with PKU were requested to give their written consent to include data from the patients' records. A regional ethics committee approved the procedure used in the studies.

The comparative study

In *Study II* the patients with PKU were compared with two other groups of patients. These two groups were chosen for special reasons. Patients with PKU get deficits in the neurobehavioral domain when their disease is left untreated. Therefore, it was important that the measure of adjustment was sensitive to neurobehavioral symptoms.

Recent studies of patients with neurobehavioral syndromes indicate that the aetiology of these syndromes is an interaction of various neuroanatomical, neurochemical, and genetic factors. The different diagnoses in the neurobehavioral spectra are related to each other. Adjustment difficulties and impairments in executive functions are emergent features (Biederman, Mick, & Faraone, 1998; Landgren, Kjellman, Gillberg, 2000; Nordin & Gillberg, 1998; Séguin, Boulerice, Harden, Tremblay, & Pihl, 1999). Symptoms arise in early childhood, are relatively chronic throughout the life span, and are frequently manifested as difficult and negative behaviours. Diagnoses are based on behavioural criteria according to DSM-IV (American Psychiatric Association, 1994).

The next group of patients in the comparison is patients with obesity. During the last years, obesity has emerged as an increasing threat towards public health (Myers & Rosen, 1999; Rasmussen, Johansson, & Hansen, 1999), and preoccupation with eating, dieting, and body image starts at an early age (Edlund, Halvarsson, & Sjödén, 1996). Patients with obesity might have some adjustment difficulties according to previous research, but to a lesser extent than patients with neurobehavioral disorders. Just as patients with PKU, the obese patients have daily concerns about their eating habits. Contrary to patients with PKU the obese patients have a visible stigma, which can have more or less influence on their behaviour and well being (Mannucci et al., 1999; Stradmeijer, Bosch, Koops, & Seidell, 2000; Valtolina & Marta, 1998).

The comparison between the three groups of patients and the healthy reference group was performed of methodological reasons. If the measures are valid, differences between the groups would be found. The extent and nature of these differences are of clinical, paediatric importance.

Participants

Patients with PKU. All PKU patients born between 1980 and 1991, totally 53 children and youths early and continuously treated, were invited to participate in the study. A total of 46 patients (27 boys and 19 girls) accepted (87%). The patients were divided into two groups according to age: 23 patients between 8 and 12 years of age and 23 patients between 13 and 19 years of age. Of the parents of these patients, 47 accepted an invitation to participate (89%), which added one more male to the oldest age group. The parents granted permission to include teachers' ratings in the data collection for 19 boys and 8 girls. Forty-two parents returned their written consent to include severity of disease, Phe level, and IQ in the data collection, N=42 for parents and N=41 for patients.

In *Study II* the youngest patients were excluded, resulting in 49 children and youths early and continuously treated. Forty-two patients (24 boys and 18 girls) participated (86%). Forty-three parents (88%) responded and added one more male to

the data collection. For 24 children permission to include teachers' ratings was granted and those teachers participated in the study.

In *Study III* 40 patients with PKU were included; those who had provided information on Phe level and were still on a special diet.

Patients with neurobehavioral disorders. *Study II* comprised patients with neurobehavioral disorders. The criteria for inclusion were that the patients had a diagnosis indicating problems in the neuropsychiatry domain; ADHD, Asperger, or mild autism. Those who were mentally retarded were not included in the present study. The patients were expected to do self-ratings, and thus be able to read and write. They were matched with the PKU patients according to gender and date of birth with a maximum deviance of four months. Thirty-six patients (73%), 21 boys and 15 girls responded and 34 (69%) parents participated. For 20 patients permission to include teachers' ratings was granted and those 20 teacher ratings were accomplished.

Patients with obesity. A sample of patients with severe overweight (>2,5 SD in weight over height) was also invited to participate in *Study II*. They were matched with the PKU patients in the same way as the patients with neurobehavioral syndromes. Forty-three patients (88%), 22 boys and 21 girls participated in the study and 42 of their parents (86%). Teachers' ratings were permitted for 23 patients and 22 of them responded.

Reference group. The non-clinical reference group in *Study I and II* comprised Swedish children and youths recruited from ten schools in five urban and rural districts. The criteria for inclusion were that the children were in the ordinary school system. Pupils who were in special education or were recently arrived refugees were excluded. The children and youths were matched with the PKU patients according to gender and date of birth, with a maximum deviance of a month. For each patient there were six or seven in the reference group living in different places.

Questionnaires for rating their children were mailed to the parents of 199 children. The response rate was 151 (75%).

A total of 170 parents were asked for permission to obtain teacher ratings. Only 79 of these teacher ratings were accomplished (46%) although teachers' ratings were allowed by written consent from 121 parents.

From the total sample of children, 296 were selected for self-ratings, and 200 complied (68%). The questionnaires were given out to the children at school and 207 parents had permitted their child to participate.

Measures

PKU severity. Severity of disease was classified using the doctors' and the dieticians' judgement of Phe tolerance at the age of five years. This classification was done without knowledge of the genotype. The genotype was determined in 26 of the patients at the Centre for Inborn Metabolic Diseases, and the severity of the mutations is known from in vitro expression studies (PAHdb). This relation supports the phenotype classification.

Phe level. The same measure of Phe level was used at three ages. The individual measures of diet were calculated as the mean level of Phe in the blood tests during the child's first year, the fourth year, and the last year preceding this investigation.

Intelligence. Results from intelligence tests (WISC) when the patients with PKU were about 8-10 years old were used in *Study I.* The scores were compared with age-appropriate Swedish norms for WISC. In recent years, there has been a general improvement in children's intelligence, and a new edition now replaces the earlier WISC scale. Patients' scores recently tested with the old version of WISC were reduced by 8 IQ points, in accordance with the new norm (Sonnander, 1990).

Adjustment. Adjustment was measured in *Study I and II*, using the multi-informant questionnaires developed for this special purpose (see pp. 20-23).

Coping. Two measures of coping were used in *Study III*, one for the parents of children with PKU and one for the patients themselves (see pp. 28-32).

General health. The participants in *Study I and II* provided information on the patients' general health. The parents could answer yes or no to indicate the presence of health problems in any of four areas, namely allergy, asthma, epilepsy, and

gastrointestinal disease. There were also two open-ended questions to add information about health problems not included in those four categories.

Social economic status. A five-point scale showing different duration of education corresponding to the Swedish educational system was used as measure of parents' social economic status. The mean of both parents' educational level was calculated for the parents in all three studies.

Civil status. The parents answered a question, whether they were living together with the child's biological parent or if they were separated/divorced. The measure of civil status was used in *Study II and III.*

Methodological considerations

The response rate in *Study II* was high among patients with PKU and patients with obesity, and lower among patients with neurobehavioral disorders and in the reference group. The patients were given two movie tickets. Patients with neurobehavioral disorders might have had difficulties filling in the questionnaire, regardless of the compensation. In the reference group the motivation to participate might have been lower without any reward.

In order to minimise the demands the reference group was divided. One group of parents rated their child, and another group was asked for permission of teacher ratings of their child. The great loss of teacher ratings in the reference group was probably due to the fact that the investigation was carried out late during the spring term.

The non-responders in the reference group were contacted via telephone call, revealing different reasons behind the dropout. Some of the parents and/or their children had a negative opinion about research projects in general and did not want to participate. Others found this study to be concerned with too personal questions, e.g. they refused because they had problems in the family and considered this study too intimate. From the total sample in the reference group, comprised of 369 families, 272 (74%) participated. The rate of dropout was 26%. A comparison of those who answered immediately and those who answered after a telephone call and/or a second letter showed no difference in mean and standard deviation in any of the factors. The

sample was thus considered representative and was used as reference group in *Study I and II*.

Notice that in *Study I* there were patients with PKU from eight years of age. These youngest children were excluded in the second study, because it was regarded too difficult for the patients with neurobehavioral disorders of that age to participate. A pilot study had indicated that the questionnaire is most appropriate for children from about nine years. Among children in general, some can have difficulties with the multiple-choice format. If the participants have cognitive deficits, the homogeneity will decrease.

A high rate of parents to the patients did not give permission to collect teacher ratings on their children. Probably the teacher ratings in *Study I and II* were given on those pupils where there was good contact between the family and the school. A higher rate of participation might have given a different result.

The coping questionnaires developed for *Study III* have shortcomings with regard to psychometric properties. A factor analysis on small samples calls for caution in the interpretation. The original questionnaires consisted of more items, and were supposed to end up in some additional coping variables. Many items were excluded in the analysis because they were conceptually unclear. For a more exhaustive study on coping a larger group of participants is needed.

Study I: Adjustment and Intelligence among Children with PKU in Sweden

Aim and method. *Study I* was an evaluation of treatment outcome among children and youths with PKU. Outcome measures were investigated in relation to predictor variables and moderators (see Figure 1).

Methods for analysis were Pearson's correlation for association between variables, Student's t-test for comparison between patients with PKU and the reference group, and for comparison between mild and severe PKU. The prevalence of health problems were compared with the non-clinical reference group with χ^2.

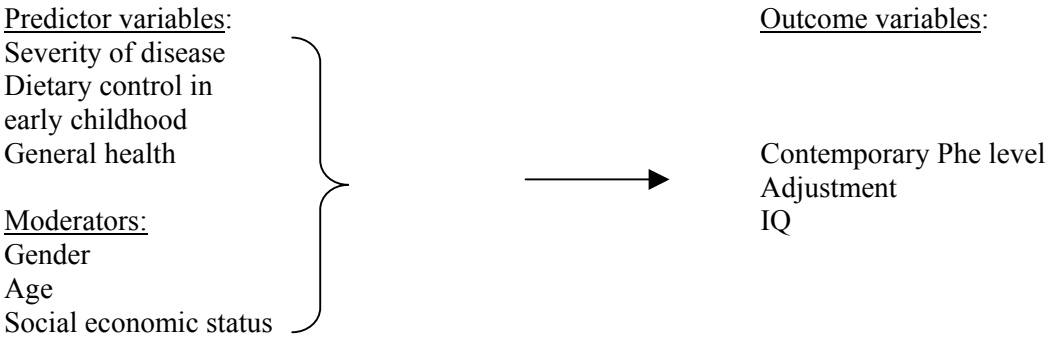

Figure 1. An explorative investigation of treatment outcome among children with PKU

Results. The results showed that both early and contemporary Phe levels in blood tests was in accordance with treatment norms, although the teen-agers had higher levels of Phe compared to the younger patients. The PKU patients did not differ from the reference group on adjustment, except for externalising problems judged by the children themselves. None of the patients with PKU showed signs of externalising problems in contrast to the reference group, where such behaviour was observed. Patients with severe PKU, however, showed less social competence compared with patients with a milder form of the disease according to their own and their parents' ratings. The results showed that development of the patients' intelligence was normal. Patients with a severe genotype had a mean IQ of 96.33 (SD=15.60, N=15) and patients with a mild genotype had a mean IQ of 103.26 (SD=16.23, N=19). No difference in general health was found between patients with PKU and the reference group. Outcome variables were associated with neither early dietary control nor gender or social economic status.

Comments. The results from the first study are mainly consistent with previous research on PKU. However, there are differences, since the present investigation showed no linear correlation between outcome measures and Phe levels at different ages. When Phe level is within the recommended range, the patients' IQ and the parents' social economic status are highly associated. Thus, we have to consider the possibility of a normal variation within specific limits as well as the fact that many different variables exert influence on brain functioning and psychosocial adjustment

(Susman, 1998). The evaluation of the PKU patients' results on WISC was made with the new Swedish norm (Sonnander, 1990) and no deviation from normal results was found contrary to most other studies (e.g. Burgard et al., 1996b, Smith et al., 1990). Differences in intelligence between severe and mild PKU did not reach significance in the present study, but the distance between the groups was the same as previously reported (Medical Research Council, 1993).

Preventive care is necessary in cases of PKU. The medical treatment does not correct the biochemical balance completely, but still the children appear normal and healthy. In individual patients, an impaired transport of Phe over the blood brain barrier may change the susceptibility of the brain for high Phe blood levels. Possibly, some of the children in the present investigation might have been normal even without dietary restrictions (Ramus et al., 1993). Studies of blood - brain Phe correlations may provide information for a more individualised therapy in the future.

Study II: Adjustment among Patients with PKU, compared with Patients with Neurobehavioral Disorders and Patients with Obesity

Aim and method. This study was an investigation of the sensitivity of the questionnaire and the applicability of the adjustment concept. *Study II* comprised two further groups of patients besides patients with PKU, where information on adjustment can be received from other studies and compared with the present results. The aim was to investigate both intrinsic and extrinsic adjustment in these three groups of patients compared with a healthy reference group. If differences between the groups are obtained, the method is considered valid. Furthermore, differences in adjustment are of clinical paediatric importance.

The comparison between the three groups of patients and the reference group was performed with analysis of variance. Before the analysis was run, a random sample was drawn from the reference group to get comparable sizes of the groups.

The prevalence of divorce was compared with the non-clinical reference group with χ^2. The comparison of social economic status was made with analysis of variance.

Results. All three groups of informants gave a convincing picture of normal adjustment among patients with PKU in the four aspects investigated. In the other groups of patients, adjustment difficulties were present to different extents. The results on each of the four variables give an exhaustive account and are presented in *Study II*.

To get a summary of the results a composed measure of adjustment can be calculated by adding the two scales labelled work capacity and social competence to the two last scales, measuring externalising and internalising problems, which then had to be reversed. In the self-rating, patients with neurobehavioral syndromes were found to be less adjusted compared with the non-clinical reference group and with patients with PKU. In the parents' ratings the patients with neurobehavioral syndromes received lower scores than the other three groups. Furthermore, obese patients received lower scores than the reference group and patients with PKU. Finally, in the teachers' ratings the patients with neurobehavioral syndromes received lower scores than the reference group and patients with PKU.

There was no difference in social economic status between the groups, but a significantly higher extent of divorce in families with children with neurobehavioral syndromes and obesity was found.

Comments. This study was informative regarding adjustment difficulties among the groups of patients subjected to this investigation; that is neurobehavioral syndromes and obesity. Although the children with different diagnoses need different treatment, there can also be some important conclusions on the rationale for paediatric care.

To achieve health, it is important to understand the individual genetic predisposition and to adapt the daily habits according to this. Research on PKU has continuously improved the diagnosis of the condition. For patients with neurobehavioral syndromes and obesity we have no single explanation for their conditions.

To treat patients with neurobehavioral syndromes or obesity, much more knowledge about the precursory conditions to their symptoms are needed. More attention needs to be paid to the individual anamnesis. The role of cognitive factors in neurobehavioral disorders has dominated research for some years, but the present study highlights the importance of social and emotional aspects. The significantly higher rate of divorce in families with children with neurobehavioral syndromes and obesity calls for attention. More knowledge about the developmental conditions in the child's family and measures of individual developmental trajectories would improve future research and treatment for those chronically ill children.

Study III: Prerequisites for diet continuation in adolescent patients with PKU

Aim and method. In *Study I* teen-agers were found to have higher levels of Phe than children had. *Study III* focuses on psychological factors associated with good adherence to the dietetic therapy. Figure 1 was extended with two mediating variables, and parents' civil status was added among the moderators, which is illustrated in Figure 2.

In *Study III* the effect of coping on Phe level was calculated with hierarchical multiple regression and the comparison of coping among patients to married or divorced parents was made with Student's t-test.

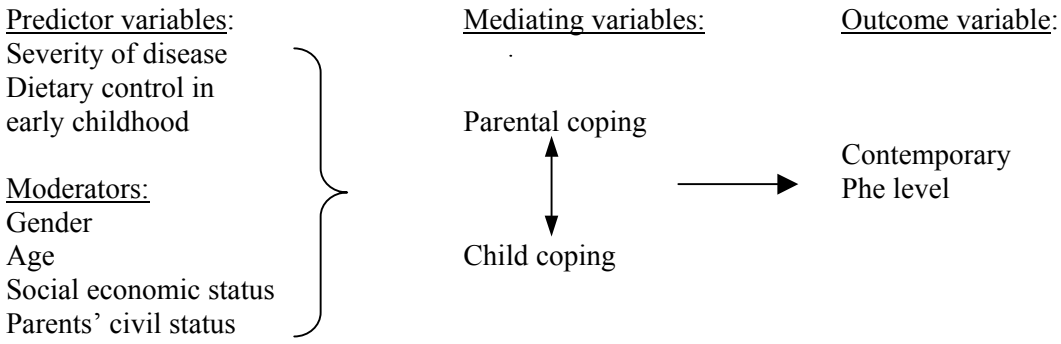

Figure 2. An investigation of coping among children and youths with PKU

Results. Severity of disease was associated with neither early nor contemporary Phe level, which means that other factors than severity of disease affects treatment outcome. Among the moderating variables, gender and social economic status were associated with neither coping nor contemporary Phe level. Differences in parents' civil status showed that dietary control during childhood and concurrent child coping were negatively affected in cases of divorce, but the contemporary Phe level was not affected.

To investigate the effect of different coping variables on contemporary Phe level, multiple analysis of regression was used. When the age variable was accounted for, parents' problem-focused coping was the main factor behind differences in compliance with the diet. There was an association between parental problem-focused coping and child support-seeking strategies. Among the children (8-12 years) there was a significantly higher level of parents' problem-focused coping and patients' support-seeking strategies, compared with the teen-agers (13-19 years).

Comments. Previous research points to the necessity for social support for diet continuation (Levy & Waisbren, 1994), but the conclusion from this study is another one. The results from the present study ought to be seen in a developmental perspective. The lower level of problem-focused coping among parents' to adolescents is a natural consequence of the youths' liberation and a change to more age-appropriate expectations. It is not realistic to give incentives to increase parents' problem-focused coping or suggest social support to the patients. Social support functions differently in chronic than in acute situations (Quittner, Glueckauf, & Jackson, 1990). For the patients, the awareness of the illness comes gradually and the transition to self-care is rather a question of education. When the children grow older, they have to take own responsibility for treatment and just as the parents once received personal advice regarding their new-born baby, the patients need to start all over again with a marked transition to self-care. To improve dietary continuation into adulthood, the patients need to learn about their disease and get assistance with metabolic control (Wendel & Langenbeck, 1996).

Implications for Clinical Psychology and Research on PKU

Psychological counselling in early childhood

Coping with PKU and its treatment have been suggested to be so complicated that paediatric control should be combined with psychological counselling (Hendrikx, van der Schot, Slijper, Huisman, & Kalverboer, 1994). The present thesis did not address this issue, yet some implications can be seen.

No signs of maladjustment were found among the patients and apparently the support from the metabolic team has been sufficient in Sweden. The children's' development is quite normal as long as dietary control is kept, and hence there is no reason to raise concerns about the patients' intellectual level during early childhood. According to *Study I*, the patients' intelligence is more highly associated with the parents' educational level than with Phe level. Rather than looking for developmental delay, the psychological assessment should focus on signs of incomplete acceptance of the child's disease in the parents. According to previous research, this might exert an influence on the child's development and adjustment (Burgard, Armbruster, Schmidt, & Rupp, 1994; Griffiths, Demellweek, Fay, Robinson, & Davidson, 2000; Pietz et al., 1997; Smith et al., 1988).

In psychological counselling it is important to analyse the nature of the transfer of emotional, cognitive, and behavioural schemas (Baumrind, 1973; Brazelton & Yogman, 1986; Bretherton & Waters, 1985; Fagot, 1998; Maccoby, 1984, & 1992). It is in the joint activity dyads that most important developmental processes take place (Kochanska, 1997; Posner & Raichle, 1994; Stern, 1985). Stressors linked to early development are those engendered by the crisis of having a child with a metabolic disease, probably evoked in the feeding situations and when taking blood tests.

The parents' capability to manage the crisis in the neonatal period is suggested to be of importance for their emotional availability (Bowlby, 1966 & 1971; Kliewer et al., 1996). When this early attachment is constituted normally, the child has some self-regulating capacity, which means resilience toward subsequent stress. Failing to cope leads to a risk that the child will be influenced by the stress of an overloaded parent

(Creasey et al., 1997; Field & Fox, 1985), which can manifest itself in at least two different ways. One is avoidance, whereby the child is left too much on its own with risk for emotional neglect. The other risk is overprotection, which can be expressed in intrusiveness, resulting in lower self-esteem in the child (Thomasgard, Metz, Edelbrock, & Shonkoff, 1995). A child's chronic disease can evoke both of these extreme reactions, with risk for subsequent adjustment problems on the child's part.

Children have different strategies for managing stress and feelings of discomfort at different ages and the age-related changes in children's coping behaviour can best be understood by Piaget's stages of mental development (Flavell, 1963; Zeman & Shipman, 1997). Just as the assessment of intelligence, coping behaviour is conceived as motor-perceptual in the beginning and later more cognitive (Losoya, Eisenberg, & Fabes, 1998). Besides normal variation in mental development, coping should also be considered in the frame of reference provided by attachment theory.

Early psychological counselling should comprise both parental support, evaluation of the emotional and social development in the child, and considerations of the triadic relationship between the child and its parents. Although most families obviously go through this period with success, it is important to identify and give support to those few and exceptional cases who are at risk for failing. They are well known in clinical practice, but easily overlooked in research focusing on the preponderant part of the patients.

Testing children and adults

The psychological concern over PKU up to date has mostly been about the measurement of intelligence. In the future also, continuous measurement with WISC at one and the same age for all Swedish children would be advantageous. When using the latest and extended version of WISC more detailed information on the patients' achievement will be provided (Kaufman, 1994). The results from the WISC III can be presented in not only verbal and performance factors, but also in "freedom from distractibility" and "speed of mental processing".

During the last years, focus has moved to neuropsychological functioning in patients with PKU. This represents an interesting area for future research, especially for evaluation of development among adults with different levels of dietary control.

Diet education programs

Developing the education of the patients to improve their self-care is important for particularly two reasons; one is the concern over the patients' own neurological health, and the other is the concern over next generation (Cechák et al., 1996; Levy & Waisbren, 1994).

Diet education programs can preferably be introduced long before the patients reach adulthood. Children are in general more receptive to compulsory education before adolescence and their habits can be adapted to diet continuation and life-long treatment as a natural follow-up of the parents' successful treatment during childhood.

Gender differences have been obvious in studies on some chronic diseases (Grey, Lipman, Cameron, & Thurber, 1997; Wayne Holden, Chmielewski, Nelson, & Kager, 1997). No gender differences appeared in the present investigation, but probably they are more plausible in adulthood. Pietz et al. (1997) showed that female patients of childbearing age had an increased frequency of functional and emotional symptoms, as well as a more negative social self-perception, possibly due to the awareness of problems of maternal PKU. The offspring of a woman with PKU runs an increased risk for microcephaly, mental retardation, heart defects, and other congenital anomalies unless the pregnant PKU woman has a highly restricted diet at the time of conception (Gross Friedman et al., 1996; Shiloh, Waisbren, Cohen, & St James, 1993). Medical and health care providers need to adapt their disease and diet education programs by addressing the concerns of the emerging adult and particularly consider the maternal PKU care in a social and cultural context.

Concluding remark

This work started with a notion of PKU as a severe disease, which without treatment leads to lifelong handicap. The main conclusion after this investigation is

that PKU is a biochemical dysfunction, which does not cause harm as long as the dietary control is kept. The children and youths with PKU in Sweden do not have any symptoms. Parents participating in this study have emphasised that they regard their child as completely healthy. The same applies to the youths' opinion about themselves.

The normal outcome among children and youths with PKU in Sweden is due to the general improvement of the treatment, but a contributing factor is probably the high and fairly equal standard of living in the Swedish society.

To cure a patient it is not enough to treat the disease; it is also important to focus on different factors contributing to the maintenance of health. With a chronic disease, the patient has to manage the treatment across the life span and the hospital staff has to adapt to different individual reactions.

In fact, the World Health Organization has underscored that man's situation in cases of disease is most appropriately described as one of interdependence (WHO, 1980). A notable feature of highly integrated societies is the extreme dependence of the individual on others. The social relations an individual enjoys are equally as essential for quality of life as is competence in attending to physiological needs. From this point of view, treatment of chronic disease can be understood as an interactive occurrence, executed by individuals in a social context, just as important for mental health as the medical treatment per se (Elman et al., 1996). Differences in the social structure in different societies may contribute to differences in treatment outcome.

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REFERENCES

Achenbach, T.M. & Edelbrock, C.S. (1979). The Child Behavior Profile: II. Boys Aged 12-16 and Girls Aged 6-11 and 12-16. *Journal of Consulting and Clinical Psychology*, *47* (2), 223-233.

Aldwin, C.M. (1994). *Stress, Coping and Development. An integrative Perspective*. The Guilford Press, New York.

Alm, J. (1981). *Evaluation of a neonatal mass screening programme in Sweden: Results and potential benefits.* Department of Paediatrics, Karolinska Institute, Stockholm.

American Psychiatric Association (1994). *Diagnostic and statistical manual of mental disorders* (4th ed.). Washington DC.

Antisdel, J.E. & Chrisler, J.C. (2000). Comparison of Eating Attitudes and Behaviors Among Adolescent and Young Women with Type 1 Diabetes Mellitus and Phenylketonuria. *Journal of Developmental and Behavioral Pediatrics, 21* (2), 81-86.

Awiszus, D. & Unger, I. (1990). Coping with PKU: results of narrative interviews with parents. *European Journal of Pediatrics*, *149* (Suppl.1), 45-51.

Ayers, T.S., Sandler, I.N., & Twohey, J.L. (1998). Conceptualization and Measurement of Coping in Children and Adolescents (Chapter 8). In Ollendick TH & Prinz RJ (Ed.) *Clinical Child Psychology*, Vol.20 Plenum Press, New York and London.

Ayers, T.S., Sandler, I.N., West, S.G., & Roosa, M.W. (1996). A Dispositional and Situational Assessment of Children's Coping: Testing Alternative Models of Coping. *Journal of Personality, 64* (4), 923-958.

Azen, C., Koch, R., Friedman, E., Wenz, E., & Fishler, K. (1996). Summary of findings from the United States Collaborative Study of children treated for phenylketonuria. *European Journal of Pediatrics, 155* (Suppl.1), 29-32.

Band, E.B. & Weisz, J.R. (1988). How to feel better when it feels bad: Children's perspectives on coping with everyday stress. *Developmental Psychology*, *24*, 247-253.

Baron, R.M. & Kenny, D.A. (1986). The Moderator-Mediator Variable Distinction in Social Psychological Research: Conceptual, Strategic, and Statistical Considerations. *Journal of Personality and Social Psychology*, *51* (6), 1173-1182.

Baumrind, D. (1973). The Development of Instrumental Competence through Socialization. In A.D. Pick (Ed.) *Minnesota Symposium on Child Psychology* . (Vol. 7, pp. 3-46) Minneapolis: University of Minnesota Press.

Belsky, J. (1984). The Determinants of Parenting: A Process Model. *Child Development, 55*, 83-96.

Berg, C.A., Meegan, S.P., & Deviney, F.P. (1998). A Social-contextual Model of Coping with Everyday Problems across the Lifespan. *International Journal of Behavioral Development 22* (2), 239-261.

Biederman, J., Mick, E., & Faraone, S.V. (1998). Normalized functioning in youths with persistent attention-deficit/hyperactivity disorder. *Journal of Pediatrics 133* (4), 544-551.

Bird, H.R., Shaffer, D., Fisher, P., Gould, M.S., Staghezza, B., Chen, J.Y., & Hoven, C. (1993). The Columbia Impairment Scale (CIS): Pilot Findings on a Measure of Global Impairment for Children and Adolescents. *International Journal of Methods in Psychiatric Research, 3,* 167-176.

Bowlby, J. (1966). *Maternal Care and Mental Health. Deprivation of Maternal Care. A Reassessment of Its Effects*. Two Volumes in One. Schocken Books, New York.

Bowlby, J. (1971). *Attachment* (Vol.1) Middlesex, UK Pelican.

Brazelton, T.B. & Yogman, M.W. (1986). *Affective development in infancy*. Ablex publishing corporation, Norwood, N.J.

Bretherton, I. & Waters, E. (1985). *Growing points of attachment*. Monographs of the Society for Research in Child Development 50 (1-2).

Bronfenbrenner, U. (1979). *The Ecology of Human Development. Experiments by Nature and Design*. Harvard University Press.

Brown, M.C.J. & Guest, J.F. (1999). Economic impact of feeding a phenylalanine-restricted diet to adults with previously untreated phenylketonuria. *Journal of Intellectual Disability Research, 43* (1), 30-37.

Burgard, P., Armbruster, M., Schmidt, E., & Rupp, A. (1994). Psychopathology of patients treated early for phenylketonuria: results of the German collaborative study of phenylketonuria. *Acta Paediatrica,* (Suppl. 407), 108-110.

Burgard, P., Bremer, H.J., Buhrdel, P., Clemens, P.C., Mönch, E., Przyrembel, H., Trefz, F.K., & Ullrich, K. (1999). Rationale for the German recommendations for phenylalanine level control in phenylketonuria 1997. *European Journal of Pediatrics, 158*, 46-54.

Burgard, P., Rupp, A., Konecki, D.S., Trefz, F.K., Schmidt, H., & Lichter-Konecki, U. (1996). Phenylalanine hydroxylase genotypes, predicted residual enzyme activity and phenotypic parameters of diagnosis and treatment of phenylketonuria. *European Journal of Pediatrics, 155* (Suppl.1), 53-55.

Burgard, P., Schmidt, E., Rupp, A., Schneider, W., & Bremer, H.J. (1996a). Intellectual development of the German Collaborative Study of children treated for phenylketonuria. *European Journal of Pediatrics, 155* (Suppl.1), 33-38.

Cabalaska, M.B., Nowaczewska, I., Sendecka, E., & Zorska, K. (1996). Longitudinal study on early diagnosis and treatment of phenylketonuria in Poland. *European Journal of Pediatrics*, *155* (Suppl.1), 53-55.

Carver, C.S., Scheier, M.F., & Weintraub, J.K. (1989). Assessing coping strategies: A theoretically based approach. *Journal of Personality and Social Psychology*, *56*, 267-283.

Cavell, T.A. (1990). Social Adjustment, Social Performance, and Social Skills: A Tri-Component Model of Social Competence. *Journal of Clinical Child Psychology, 19* (2), 111-122.

Cechák, P., Hejcmanová, L., & Rupp, A. (1996). Long-term follow-up of patients treated for phenylketonuria (PKU). Results from the Prague PKU Center. *European Journal of Pediatrics*, *155* (Suppl.1), 59-63.

Cerone, R., Schiaffino, M.C., Di Stefano, S., & Veneselli, E. (1999). Phenylketonuria: diet for life or not? *Acta Paediatrica, 88*, 664-666.

Chang, P.N., Gray, R.M., O'Brien, L.L. (2000). Patterns of academic achievement among patients treated early with phenylketonuria. *European Journal of Pediatrics, 159* (Suppl. 2), 96-99.

Cleary, M.A., Walter, J.H., Wraith, J.E., Jenkins, J.P.R., Alani, S.M., Tyler, K., Whittle, D. (1994). Magnetic resonance imaging of the brain in phenylketonuria. *Lancet, 344*, 87-90.

Compas, B.E. (1998). An Agenda for Coping Research and Theory: Basic and Applied Developmental Issues. *International Journal of Behavioral Development, 22* (2), 231-237.

Compas, B.E., Banez, G.A., Malcarne, V., & Worsham, N. (1991). Perceived Control and Coping with Stress: A Developmental Perspective. *Journal of Social Issues* , *47* (4), 23-34.

Compas, B., Malcarne, V., & Fondacaro, K. (1988). Coping with Stressful Events in Older Children and Young Adolescents. *Journal of Consulting and Clinical Psychology*, *56* (3), 405-411.

Creasey, G., Ottlinger, K., DeVico, K., Murray, T., Harvey, A., & Hesson-McInnis, M. (1997). Children's Affective Responses, Cognitive Appraisals and Coping Strategies in Response to the Negative Affect of Parents and Peers. *Journal of Experimental Child Psychology, 67*, 39-56.

Diamond, A., Prevor, M.B., Callender, G., & Druin, D.P. (1997). Prefrontal Cortex Cognitive Deficits in Children Treated Early and Continuously for PKU. *Monographs of the Society for Research in Child Development*, *252*, 62 (4).

Duran, G.P., Rohr, F.J., Slonim, A., Guttler, F., & Levy, H.L. (1999). Necessity of complete intake of phenylalnine-free amino acid mixture for metabolic control of phenylketonuria. *Journal of the American Dietetic Association, 99* (12), 1559-1563.

Edlund, B., Halvarsson, K., & Sjödén, P.O. (1996). Eating Behaviours, and Attitudes to Eating, Dieting, and Body Images in 7-year-old Swedish Girls. *European Eating Disorders Review, 4* (1), 40-53.

Elman, J.L., Bates, E.A., Johnson, M.H., Karmiloff-Smith, A., Parisi, D., & Plunkett, K. (1996). *Rethinking innateness.* (chap. 1, 3, 5) Cambridge MA: MIT Press.

Fagot, B.I. (1998). Social Problem Solving: Effect of Context and Parent Sex. *International Journal of Behavioral Development* ,*22* (2), 389-401.

Farrell Erickson, M., Sroufe, L.A., & Egeland, B. (1985). The relationship between quality of attachment and behavior problems in preschool in a high-risk sample. In I. Bretherton & E. Waters (Eds.) *Growing points of attachment theory and research.* (pp. 147-166) Monographs of the Society for research in child development, Chicago.

Fisch, R.O., Matalon, R., Weisberg, S., & Michals, K. (1997). Phenylketonuria: Current Dietary Treatment Practices in the United States and Canada. *Journal of the American College of Nutrition, 16* (2),147-151.

Field, T.M. & Fox, N.A., Eds. (1985). *Social Perception in Infants.* Ablex publishing corporation, Norwood, New Jersey.

Flavell, J.H. (1963). *The developmental psychology of Jean Piaget.* (pp. 15-84) New York: D. Van Nostrand Co.

Frank, R.G., Thayer, J.F., Hagglund, K.J., Vieth, A.Z., Schopp, L.H., Beck, N.C., Kashani, J.H., Goldstein, D.E., Cassidy, J.T., Clay, D.L., Chaney, J.M., Hewett, J.E., & Johnson, J.C. (1998). Trajectories of Adaptation in Pediatric Chronic Illness: The Importance of the Individual. *Journal of Consulting and Clinical Psychology*, *66* (3), 521-532.

Freitas, A.L. & Downey, G. (1998). Resilience: A Dynamic Perspective. *International Journal of Behavioral Development, 22* (2), 263-285.

Fritz, G.K., McQuaid, E.L., Spirito, A., & Klein, R.B. (1996). Symptom Perception in Pediatric Asthma: Relationship to Functional Morbidity and Psychological Factors. *Journal of American Academy Child and Adolescent Psychiatry*, *35* (8), 1033-1041.

Gardner, H. (1993). *Multiple Intelligences*. The Theory in Practice. Basic Books, New York.

Greeves, L.G., Patterson, C.C., Carson, D.J., Thom, R., Wolfenden, M.C., Zschocke, J., Graham, C.A., Nevin, N.C., & Trimble, E.R. (2000). Effect of genotype on changes in intelligence quotient after dietary relaxation in phenylketonuria and hyperphenylalaninaemia. *Archives of Disease in Childhood, 82* (3), 216-221.

Grey, M., Cameron, M.E., & Thurber, F.W. (1991). Coping and Adaptation in Children with Diabetes. *Nursing Research*, *40* (3), 144-149.

Grey, M., Lipman, T., Cameron, M.E., & Thurber, F.W. (1997). Coping Behaviors at Diagnosis and in Adjustment One Year Later in Children With Diabetes. *Nursing Research*, *46* (6), 312-317.

Griffiths, P.V., Demellweek, C., Fay, N., Robinson, P.H., & Davidson, D.C. (2000). Wechsler subscale IQ and subtest profile in early treated phenylketonuria. *Archives of Disease in Childhood, 82* (3), 209-215.

Griffiths, P., Paterson, L., & Harvie, A. (1995). Neuropsychological effect of subsequent exposure to phenylalanine in adolescents and young adults with early-treated phenylketonuria. *Journal of Intellectual Disability Research, 39* (5), 365-372.

Griffiths, P., Smith, C., & Harvie, A. (1997). Transitory Hyperphenylalaninaemia in Children With Continuously Treated Phenylketonuria. *American Journal on Mental Retardation, 102* (1), 27-36.

Griffiths, P., Tarrini, M., & Robinson, P. (1997a). Executive function and psychosocial adjustment in children with early treated phenylketonuria: Correlation with historical and concurrent phenylalanine levels. *Journal of Intellectual Disability Research, 41* (4), 317-323.

Gross Friedman, E., Azen, C., Levy, H., Hanley, W., Matalon, R., Ronse, B., Trefz, F., & de la Cruz, F. (1996). The International Collaborative Study on maternal phenylketonuria: organization, study design and description of the sample. *European Journal of Pediatrics*, *155* (Suppl.1), 158-161.

Guthrie, R. & Susi, A. (1963). A simple phenylalanine method for detection of phenylketonuria in large populations of newborn infants. *Pediatrics*, *32*, 338-345.

Guthrie, R. (1996). The introduction of newborn screening for phenylketonuria. A personal history. *European Journal of Pediatrics* , *155* (Suppl.1), 4-5.

Guttler, F. & Guldberg, P. (1996). The influence of mutations on enzyme activity and phenylalanine tolerance in phenylalanine hydroxylase deficiency. *European Journal of Pediatrics*, *155* (Suppl.1), 6-10.

Hamlett, K.W., Pellegrini, D.S., & Katz, K.S. (1992). Childhood Chronic Illness as a Family Stressor. *Journal of Pediatric Psychology* , *17* (1), 33-47.

Harter, S. (1982). The Perceived Competence Scale for Children. *Child Development, 53*, 87-97.

Harris, E.S., Canning, R.D., & Kelleher, K.J. (1996). A Comparison of Measures of Adjustment, Symptoms, and Impairment among Children with Chronic Medical Conditions. *Journal of American Academy of Child and Adolescent Psychiatry, 35* (8), 1025-1032.

Henderson, R.M., McCulloch, D.L., Herbert, A.M., Robinson, P.H., & Taylor, M.J. (2000). Visual event-related potentials in children with phenylketonuria. *Acta Paediatrica, 89*, 52-57.

Hendrikx, M.M., van der Schot, L.W., Slijper, F.M., Huisman, J., & Kalvboer, A.F. (1994). Phenylketonuria and some aspects of emotional development. *European Journal of Pediatrics*, *153,* (11), 832-835.

Hentinen, M. & Kyngäs, H. (1998). Factors associated with the adaptation of parents with a chronically ill child. *Journal of Clinical Nursing, 7*, 316-324.

Holmbeck, G.N. (1997). Toward Terminological, Conceptual, and Statistical Clarity in the Study of Mediators and Moderators: Examples From the Child-Clinical and Pediatric Psychology Literatures. *Journal of Consulting and Clinical Psychology*, *65* (4), 599-610.

Howells Wrobel, N. & Lachar, D. (1998). Validity of Self- and Parent-report Scales in Screening Students for Behavioral and Emotional Problems in Elementary School. *Psychology in the Schools, 35* (1), 17-27.

Kalat, J.W. (1995). Biological Psychology (5th ed.), *Development and Evolution of the Brain* (chap. 5). Brooks/Cole Publ. Company.

Kalverboer, A.F., van der Schot, L.W.A., Hendrikx, M.M.H., Huisman, J., Slijper, F.M.E., & Stemerdink, B.A. (1994). Social Behaviour and task orientation in early-treated PKU. *Acta Paediatrica,* (Suppl. 407), 104-105.

Kaufman, A.S. (1994). *Intelligent testing with the WISC III.* John Wiley and Sons, New York.

Kliewer, W., Fearnow, M.D., & Miller, P.A. (1996). Coping Socialization in Middle Childhood: Test of Maternal and Paternal Influences. *Child Development*, *67*, 2339-2357.

Koch, R., Moats, R., Guttler, F., Guldberg, P., & Nelson, Jr, M. (2000). Blood-Brain Phenylalanine Relationships in Persons With Phenylketonuria. *Pediatrics*, *106* (5), 1093-1096.

Kochanska, G. (1997). Mutually Responsive Orientation between Mothers and Their Young Children: Implications for Early Socialization. *Child Development*, *68,* (1), 94-112.

Kortlander, E., Kendall, P.C., & Panichelli-Mindel, (1997). Maternal Expectations and Attributions about Coping in Anxious Children. *Journal of Anxiety Disorders*, *11,* (3), 297-315.

Landgren, M., Kjellman, B., & Gillberg, C. (2000). Deficits in attention, motor control and perception (DAMP): a simplified school entry examination. *Acta Paediatrica, 89*, 302-309.

Lazarus, R.S. & Folkman, S. (1984). *Stress, Appraisal and Coping*. Springer Publishing Company, New York.

Legido, A., Tonyes, L., Carter, D., Schoemaker, A., Di George, A., & Grover, W.D. (1993). Treatment variables and intellectual outcome in children with classic phenylketonuria: A single-center based study. *Clinical Pediatrics*, *32*, (7), 417-425.

Leuzzi, V., Bianchi, M.C., Tosetti, M., Carducci, C.L., Carducci, C.A., & Antonozzi, I. (2000). Clinical significance of brain phenylalanine concentrations assessed by in vivo proton magnetic resonance spectroscopy in phenylketonuria. *Journal of Inherited Metabolic Disease 23*, (6), 563-570.

Levy, H.L. & Waisbren, S.E. (1994). PKU in adolescents: rationale and psychosocial factors in diet continuation. *Acta Paediatrica*, (Suppl. 407), 92-97.

Losoya, S., Eisenberg, N., & Fabes, R.A. (1998). Developmental Issues in the Study of Coping. *International Journal of Behavioral Development, 22*, (2), 287-313.

Maccoby, E.E. (1984). Socialization and Developmental Change. *Child Development, 55,* 317-328.

Maccoby, E.E. (1992). The Role of Parents in the Socialization of Children: An Historical Overview. *Developmental Psychology*, *28,* (6), 1006-1017.

Magnusson, D., Dunér, A., & Zetterblom, G. (1975). *Adjustment. A longitudinal study.* Almqvist & Wiksell, Stockholm.

Magnusson, D. & Stattin, H. (1996). *Person-context interaction theories*. Reports from the Department of Psychology, Stockholm University, Number 824.

Mailick, M.D., Holden, G., & Walther, V.N. (1994). Coping with childhood asthma: Caretakers Views. *Health & Social Work, 19,* (2), 103-110.

Main, M., Kaplan, N., & Cassidy J. (1985). Security in infancy, childhood, and adulthood: a move to the level of representation. In I. Bretherton & E. Waters (Eds.) *Growing points of attachment theory and research.* (pp. 66-104) Monographs of the Society for research in child development, Chicago.

Mannucci, E., Ricca, V., Barciulli, E., Di Bernardo, M., Travaglini, R., Cabras, P.L., & Rotella, C.M. (1999). Quality of life and overweight: the obesity related well-being (ORWELL 97) questionnaire. *Addictive Behavior, 24*, (3), 345-357.

Marholin, D., Pohl, R.E., Stewart, R., Touchette, P.E., Townsend, N.M., & Kolodny, E.H. (1978). Effects of diet and behavior therapy on social and motor behavior of retarded phenylketonuric adults: an experimental analysis. *Pediatric Research, 12*, 179-187.

Medical Research Council Working Party Phenylketonuria (1993). Phenylketonuria due to phenylalanin hydroxylase deficiency: An unfolding story. *British Medical Journal*, *306*, 115-119.

Meltzoff, A.N. (1985). The Roots of Social and Cognitive Development: Models of Man's Original Nature. In Field, T.M. & Fox, N.A. (Eds.) *Social Perception in Infants.* (pp. 1-30) Ablex publishing corporation, Norwood, New Jersey.

Messick, S. (1995). Validity of Psychological Assessment. Validation of Inferences From Persons' Responses and Performances as Scientific Inquiry Into Score Meaning. *American Psychologist, 50*, (9), 741-749.

Miller, P.A., Kliewer, W., Hepworth, J.T., & Sandler, I.N. (1994). Maternal Socialization of Children's Postdivorce Coping: Development of a Measurement Model. *Journal of Applied Developmental Psychology, 15*, 457-487.

Motzfeldt, K., Lilje, R., & Nylander, G. (1999). Breastfeeding in phenylketonuria. *Acta Paediatrica,* (Suppl. 88), 25-27.

Murray, L. & Trevarthen, C. (1985). Emotional Regulation of Interactions Between Two-month-olds and Their Mothers. In Field, T.M. & Fox, N.A. (Eds.) *Social Perception in Infants.* (pp. 177-197) Ablex publishing corporation, Norwood, New Jersey.

Myers, A. & Rosen, J.C. (1999). Obesity stigmatization and coping relation to mental health symptoms, body-images and self-esteem. *International Journal of Obesity Related Metabolic Disorders, 23* (3), 221-230.

Möller, H.E., Ullrich, K., & Weglage, J. (2000). In vivo proton magnetic resonance spectroscopy in phenylketonuria. *European Journal of Pediatrics, 159*, 121-125.

Nordin, V. & Gillberg, C. (1998). The long-term course of autistic disorders: update on follow-up studies. *Acta Psychiatrica Scandinavia*, *97*, (2), 99-108.

Olson, A.L., Johansen, S.G., Powers, L.E., Pope, J.B., & Klein, R.B. (1993). Cognitive Coping Strategies of Children with Chronic Illness. *Journal of Developmental and Behavioral Pediatrics,* 14(4), 217-223.

Paans, A.M.J., Pruim, J., Smit, G.P.A., Visser, Willemsen, A.T.M., & Ullrich, K. (1996). Neurotransmitter positron emission tomographic - studies in adults with phenylketonuria. A pilot study. *European Journal of Pediatrics, 155* (Suppl.1), 78-81.

PAHdb.http://data.mch.mcgill.ca/pahdb_new

Pavone, L., Meli, C., Nigro, F., & Lisi, R. (1993). Late diagnosed phenylketonuria patients: Clinical presentation and results of treatment. *Developmental Brain Dysfunction*, *6* (1-3), 184-187.

Pietz, J., Fatkenheuer, B., Burgard, P., Armbruster, M., Esser, G., & Schmidt, H. (1997). Psychiatric disorders in adult patients with early-treated phenylketonuria. *Pediatrics, 99,* (3), 345-350.

Pietz, J., Schmidt, E., Matthis, P., Kobialka, B., Kutscha, A., & de Sonneville, L. (1993). EEGs in phenylketonuria: I.Follow-up to adulthood: II.Short-term diet-related changes in EEGs and cognitive function. *Developmental Medicine and Child Neurology, 35*, (1), 54-64.

Posner, M.I. & Raichle, M.E. (1994). Images of mind. *Brain Develops Mind* (chap. 8). New York: Scientific American Library.

Quine, L. & Rutter, D.R. (1994) First Diagnosis of Severe Mental and Physical Disability: A Study of Doctor-Parent Communication. *Journal of Child Psychology and Psychiatry, 35*, (7) 1273-1287.

Quittner, A.L., Glueckauf, R.L., & Jackson, D.N. (1990). Chronic Parenting Stress: Moderating versus Mediating Effects of Social Support. *Journal of Personality and Social Psychology, 59,* (6), 1266-1278.

Ramus, S.J., Forrest, S.M., Pitt, D.B., Saleeba, J.A., & Cotton, R.G.H. (1993). Comparison of genotype and intellectual phenotype in untreated PKU patients. *Journal of Medical Genetics, 30,* 401-405.

Rasmussen, F., Johansson, M., & Hansen, H.O. (1999). Trends in overweight and obesity among 18-year-old males in Sweden between 1971-1995. *Acta Paediatrica, 88,* 431-437.

Reid, G.J., Dubon, E.F., Carey, T.C., & Dura, J.R. (1994). Contribution of Coping to Medical Adjustment and Treatment Responsibility among Children and Adolescents with Diabetes. *Journal of Developmental and Behavioral Pediatrics, 15*, (5), 327-335.

Rey, F., Abadie, V., Plainguet. F., & Rey, J. (1996). Long-term follow up of patients with classical phenylketonuria after diet relaxation at 5 years of age. The Paris Study. *European Journal of Pediatrics*, *155* (Suppl.1), 45-49.

Robinson, M., White, F.J., Cleary, M.A., Wraith, E., Lam, W.K. & Walter, J.H. (2000). Increased risk of vitamin B12 deficiency in patients with phenylketonuria on an unrestricted or relaxed diet. *Journal of Pediatrics, 136,* 545-547.

Rupp, A. & Burgard, P. (1995). Comparison of different indices of dietary control in phenylketonuria. *Acta Paediatrica, 84*, 521-527.

Rydell, A-M., Hagekull, B., & Bohlin, G. (1997). Measurement of Two Social Competence Aspects in Middle Childhood. *Developmental Psychology, 33,* (5), 824-833.

Sandler, I.N., Tein, J-Y., & West, S.G. (1994). Coping, Stress, and the Psychological Symptoms of Children of Divorce: A Cross-sectional and Longitudinal Study. *Child Development, 65*, 1744-1763.

Scheibenreiter, S., Tiefenthaler, M., Hinteregger, V., Strobl, W., Muhl, A., Ewald, A., & Schadler, M. (1996). Austrian report on longitudinal outcome in phenylketonuria. *European Journal of Pediatrics, 155* (Suppl.1), 45-49.

Schmidt, H., Burgard, P., Pietz, J., & Rupp, A. (1996). Intelligence and professional career in young adults treated early for phenylketonuria. *European Journal of Pediatrics, 155* (Suppl.1), 97-100.

Schmidt, E., Burgard, P., & Rupp, A. (1996). Effects of concurrent phenylalanine levels on sustained attention and calculation speed in patients treated early for phenylketonuria. *European Journal of Pediatrics*, *155* (Suppl.1), 82-86.

Schmidt, E., Rupp, A., Burgard, P., Pietz, J., Weglage, J., de Sonneville, L. (1994). Sustained attention in adult phenylketonuria: The influence of the concurrent phenylalanine blood level. *Journal of Clinical and Experimental Neuropsychology*, *16*, (5), 681-688.

Schuler, A., Somogyi, Cs., Torös, I., Pataki, L., Máté, M., Kiss, E., & Nagy, A. (1996). A longitudinal study of phenylketonuria based on the data of the Budapest Screening Center. *European Journal of Pediatrics, 155*, (Suppl.1), 50-52.

Schulpis, K.H., Platokouki, E.D., Papakonstantinou, E.D., Adamtziki, E., Bargeliotis, A., Aronis, S. (1996). Haemostatic variables in phenylketonuric children under dietary treatment. *Journal of Inherited Metabolic Diseases, 19*, (5), 603-609.

Schulz, B. & Bremer, H.J. (1995). Nutrient intake and food consumption of adolescents and young adults with phenylketonuria. *Acta Paediatrica, 84*, 743-748.

Seashore, M.R., Wappner, R., Cho, S., & de la Cruz, F. (1999). Development of Guidelines for Treatment of Children With Phenylketonuria: Report of a Meeting at the National Institute of Child Health and Human Development Held August 15, 1995, National Institutes of Health, Bethesda, Maryland. *Pediatrics, 104,* (6), 1-3.

Séguin, J.R., Boulerice, B., Harden, P.W., Tremblay, R.E., & Pihl, R.O. (1999). Executive Functions and Physical Aggression after Controlling for Attention Deficit Hyperactivity Disorder, General Memory, and IQ. *Journal of Child Psychology and Psychiatry*, *40,* (8), 1197-1208.

Shiloh, S., Waisbren, S.E., Cohen, B.E., & St. James, P. (1993). Cross-cultural perspectives on coping with the risks of maternal phenylketonuria. *Psychology and health*, *8,* (6), 435-446.

Simons, R.L., Lorenz, F.O., Wu, C-I., & Conger, R.D. (1993). Social Network and Marital Support as Mediators and Moderators of the Impact of Stress and Depression on Parental Behavior. *Developmental Psychology, 29,* (2), 368-381.

Singh, R. H., Kable, J.A., Guerrero, N.V., Sullivan, K.M., & Elsas II, L.J. (2000). Impact of a camp experience on phenylalanine levels, knowledge, attitudes, and health beliefs relevant to nutrition management of phenylketonuria in adolescent girls. *Journal of the American Dietetic Association, 100,* (7), 797-803.

Skinner, E. & Edge, K. (1998). Reflections on Coping and Development across the Lifespan. *International Journal of Behavioral Development, 22*, (2), 357-366.

Smedje, H., Broman, J.E., Hetta, J., & von Knorring, A.L. (1999). Psychometric properties of a Swedish version of the ”Strengths and Difficulties Questionnaire”. *European Child & Adolescent Psychiatry, 8,* 63-70.

Smith, I., Beasley, M.G., & Ades, A.E. (1990). Intelligence and quality of dietary treatment in phenylketonuria. *Archives of Disease in Childhood*, *65,* 472-478.

Smith, I., Beasley, M.G., Wolff, O.H., & Ades, A.E. (1988). Behavior disturbance in 8-year old children with early treated phenylketonuria. *Journal of Pediatrics*, *112*, 403-408.

Sonnander K. (1990). Prevalence of Mental Retardation: An Empirical Study of an Unselected School Population. In William Fraser (Ed.) *Key issues in Mental Retardation Research* (pp. 12-18) Routledge, London.

Spirito, A., Stark, L.J., Gil, K.M., & Tyc, V.L. (1995). Coping with Everyday and Disease-Related Stressors by Chronically Ill Children and Adolescents. *Journal of the American Academy of Child and Adolescent Psychiatry*, *34,* (3), 283-290.

Sroufe, L.A. & Rutter, M. (1984). The Domain of Developmental Psychopathology. *Child Development, 55*, 17-29.

Stemerdink, B.A., van der Molen, M.W., Kalverboer, A.F., van der Meere, J.J., Hendrikx, M.M., Huisman, J., van der Schot, L.W., & Slijper, F.M. (1994). Information processing deficits in children with early and continuously treated phenylketonuria? *Acta Paediatrica,* (Suppl. 407), 106-107.

Stemerdink, B.A. (1996). *Early and continuously treated phenylketonuria. An experimental neuropsychological approach*. Faculteit der Psychologie, Universiteit van Amsterdam.

Stern, D. (1985). *The Interpersonal World of the Infant. A View from Psychoanalysis and Developmental Psychology*. Basic Books, Inc., New York.

Stern, D.N., Hofer, L., Haft, W., & Dore, J. (1985). Affect Attunement: The sharing of feeling states between mother and infant by means of inter-modal fluency. In Field, T.M. & Fox, N.A. (Eds.) *Social Perception in Infants.* (pp. 249-268) Ablex publishing corporation, Norwood, New Jersey.

Sternberg, R.J. (1990). *Metaphors of mind. Conceptions of the Nature of Intelligence*. Cambridge University Press.

Stradmeijer, M., Bosch, J., Koops, W., & Seidell, J. (2000). Family Functioning and Psychosocial Adjustment in Overweight Youngsters. *International Journal of Eating Disorders*, *27,* (1), 110-114.

Susman, E.J. (1998). Biobehavioural Development: An Integrative Perspective. *International Journal of B.ehavioral Development, 22,* (4), 671-679.

Svensson, E., von Döbeln, U., Eisensmith, R.C., Hagenfeldt, L., & Woo, S.L.C. (1993). Relation between genotype and phenotype in Swedish phenylketonuria and hyperphenylalaninemia patients. *European Journal of Pediatrics, 152*, 132-139.

Thomasgard, M., Metz, W.P., Edelbrock, C., & Shonkoff, J.P. (1995). Parent-Child Relationship Disorders. Part I. Parental Overprotection and the Development of the Parent Protection Scale. *Journal of Developmental and Behavioral Pediatrics, 16,* (4), 244-250.

Thompson Jr, R.J. & Gustafson, K.E. (1996). *Adaptation to Chronic Childhood Illness*. American Psychological Association.

Valtolina, G. & Marta, E. (1998). Family relations and psychosocial risk in families with an obese adolescent. *Psychological Reports, 83,* 251-260.

Vaz-Osorio, R., Vilarinho, L., Carmona, C., & Almeida, M. (1993). Phenylketonuria in Portugal: Multidisciplinary approach. *Developmental Brain Dysfunction*, *6*, (1-3), 78-82.

Waisbren, S.E., Brown, M.J., de Sonneville, L.M.J., & Levy, H.L. (1994). Review of neuropsychological functioning in treated phenylketonuria: an information processing approach. *Acta Paediatrica,* (Suppl. 407), 98-103.

Wappner, R., Cho, S., Kronmal, R.A., Schuett, V., & Seashore, M.R. (1999). Management of Phenylketonuria for Optimal Outcome: A Review of Guidelines for Phenylketonuria Management and a Report of Surveys of Parents, Patients, and Clinic Directors. *Pediatrics, 104*, (6), 4-9.

Wayne Holden, E., Chmielewski, D., Nelson, C.C., & Kager, V. (1997) Controlling for General and Disease-Specific Effects in Child and Family Adjustment to Chronic Childhood Illness. *Journal of Pediatric Psychology, 22*, (1), 15-27.

Weglage, J., Funders, B., Ullrich, K., Rupp, A., & Schmidt, E. (1996). Psychosocial aspects in phenylketonuria. *European Journal of Pediatrics*, *155,* (Suppl.1), 101-104.

Weglage, J., Funders, B., Wilken, B., Schubert, D., & Ullrich, K. (1993). School performance and intellectual outcome in adolescents with phenylketonuria. *Acta Paediatrica, 81*, 582-586.

Weglage, J., Pietsch, M., Feldmann, R., Koch, H.G., Zschocke, J., Hoffman, G., Muntau-Heger, A., Denecke, J., Guldberg, P., Gűttler, F., Möller, H., Wendel, U., Ullrich, K., & Harms, E. (2001). Normal Clinical Outcome in Untreated Subjects with Mild Hyperphenylalaninemia. *Pediatric Research, 49,* 532-536.

Weglage, J., Ullrich, K., Pietsch, M., Funders, B., Zass, R., & Koch, H.G. (1996). Untreated non-Phenylketonuric-hyperphenylalaninaemia: intellectual and neurological outcome. *European Journal of Pediatrics*, *155,* (Suppl.1), 26-28.

Welsh, M.C. (1996). A prefrontal dysfunction model of early-treated phenylketonuria. *European Journal of Pediatrics 155,* (Suppl.1), 87-89.

Wendel, U. & Langenbeck, U. (1996). Towards self-monitoring and self-treatment in phenylketonuria - a way to better diet compliance. *European Journal of Pediatrics, 155,* (Suppl.1), 105-107.

WHO (1980). *International classification of impairments, disabilities, and handicaps*. World Health Organization, Geneva.

Wickelgren, I. (1997). Getting the Brain's Attention. *Science, 278*, 35-37.

Wingenfeld, S.A., Lachar, D., Gruber, C.P., & Kline, R.B. (1998). Development of the teacher-informant student behavior survey. *Journal of Psychoeducational Assessment, 16*, 226-249.

Yannicelli, S. & Ryan, A. (1995). Improvements in behaviour and physical manifestations in previously untreated adults with phenylketonuria using phenylalanine-restricted diet: a national survey. *Journal of Inherited Metabolic Disease, 18*, 131-134.

Zeidner, M. & Endler, N.S. (1996). *Handbook of coping. Theory, research, applications*. John Wiley & Sons, Inc. New York.

Zeman, J. & Shipman, K. (1997). Social-Contextual Influences on Expectancies for Managing Anger and Sadness: The Transition From Middle Childhood to Adolescence. *Developmental Psychology*, *33* (6), 917-924.

Zeman, J., Pijackova, A., Behulova., Urge, O., Saligova, D., & Hyanek, J. (1996). Intellectual and school performance in adolescents with phenylketonuria according to their dietary compliance. The Czech-Slovak Collaborative Study. *European Journal of Pediatrics ,155,* (Suppl.1), 56-58.