

## OBSERVED BEHAVIOUR OF A WOMAN WITH A CHILDHOOD DIAGNOSIS OF PHENYLKETONURIA AND A PROFOUND LEARNING DISABILITY

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### Introduction

Classical phenylketonuria (PKU) is an autosomal recessive, inborn error of metabolism (Pueschel *et al.*, 1977). Due to a genetically altered enzyme (phenylalanine hydroxylase), phenylalanine is not metabolised to tyrosine. Subsequent accumulation of phenylalanine and/or its metabolites interferes with normal development of the central nervous system, often leading to microcephaly, seizures, learning disabilities, personality changes and other system involvements (Waisbren *et al.*, 1984; Thompson *et al.*, 1990). By introduction of a phenylalanine-restricted diet in the neonatal period and maintenance of such a diet during early childhood years, damage to neural tissues and other manifestations can be prevented and physical growth and intellectual maturation can usually be expected (Kron, 1972).

Debate among researchers and clinicians continues over the exact age when the phenylalanine-restricted diet should cease. Some researchers (e.g. Bickel and Gruter, 1963; Hudson, 1967) believe that the diet should be continued indefinitely throughout adulthood. Indeed, Scriver and Rosenberg (1973) emphasise that there is no real justification for discontinuing the phenylalanine-restricted diet in the pre-school child except for social convenience. The authors suggest that firm evidence has not been established for the discontinuation at usually 4-6 years of age in the USA nor that phenylalanine can perturb the chemical basis of learning later in childhood.

Kang *et al.* (1970) and also Yu and O'Halloran (1978) cite clinics that advise parents to discontinue the diet in boys with classical PKU when they enter school. Girls, however, are kept on the phenylalanine-restricted diet since

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dietary management is considered to be even more important in these patients during childbearing. Proponents for discontinuation of the phenylalanine-restricted diet in all children on entering school point to the difficulties in maintaining an older child on this diet, to the limitations of normal socialisation and peer relationship, and to the secondary emotional consequences (Horner *et al.*, 1962; Vandeman, 1963; McBean and Stephenson, 1968).

Several authors also emphasise that early termination of the diet seems to improve behaviour, school performance, and the emotional climate within the family and the PKU children gain in emotional maturity, independence and self-confidence after a regular diet is introduced (Solomons *et al.*, 1966; Hackney *et al.*, 1968; Bentovim, 1968). Others discuss the neuropathological consequences of early treatment (e.g. Welsh *et al.*, 1990; Thompson *et al.*, 1991); and Holtzman *et al.* (1975) find no evidence of deterioration of intellectual abilities after the diet has been discontinued.

A working group convened by the Medical Research Council (MRC 1993a) reviewed the current knowledge on phenylketonuria due to phenylalanine hydroxylase deficiency (MRC, 1993b). The subtle but global intellectual impairments which have been documented are, to a very substantial degree, determined in the pre-school years, long before there is any question of ceasing or relaxing treatment. The Working Party suggests that the impairments are much more closely linked with the quality of phenylalanine control than previously

recognised and there appear to be two components to this association. General ability is closely associated with phenylalanine control in the pre-school years and to a lesser extent to pre-adolescent years. In addition, performance on executive tasks depends on current phenylalanine control.

A further link between neurological status and phenylalanine control is now emerging. In untreated people with phenylketonuria undergoing magnetic resonance imaging (MRI), myelin structure has been shown to be abnormal in a high proportion of older children and adolescents with phenylalanine concentrations greater than 400-500 micromols per litre (MRC, 1993b). The greatest changes were seen in those with the highest phenylalanine concentrations. Overt neurological deterioration has been described in a few people who have shown even more marked changes on MRI.

Several studies that have mentioned blood phenylalanine levels and intelligence quotients find that there was a decrease in performance (and IQ level) on tests in children younger than 18 months when blood phenylalanine levels were below 5mg per 100ml, raising the question of whether phenylalanine needs of phenylketonuric infants are greater than normal infants and older children (Fuller and Shuman, 1971; Smith *et al.*, 1990). Neurological defects, such as epilepsy (Thompson *et al.*, 1992) and behavioural abnormalities were found to predominate in an institutional group of phenylketonurics (averaging 2.2 symptoms per case) versus a group

of patients who lived in their own home (0.26 symptoms per case) in the Pitt (1971) study. Aggressive and destructive behaviour, withdrawn and unresponsive behaviour and hyperactive behaviour, seemed to be characteristic of phenylketonuria patients when compared with others with learning disabilities who did not have phenylketonuria. These behavioural characteristics, together with blood phenylalanine levels, are the focus of this paper.

## Method

### *Client*

VW was a 39 year old woman who had been diagnosed during childhood as having classical phenylketonuria. She was resident in an establishment in the UK that cared for people with learning disabilities. She attended a local day centre once a week for sensory stimulation work and had occasional visitors who were relatives. Generally, she did not participate in activities in the home and showed no apparent interest or requests for group participation in activities.

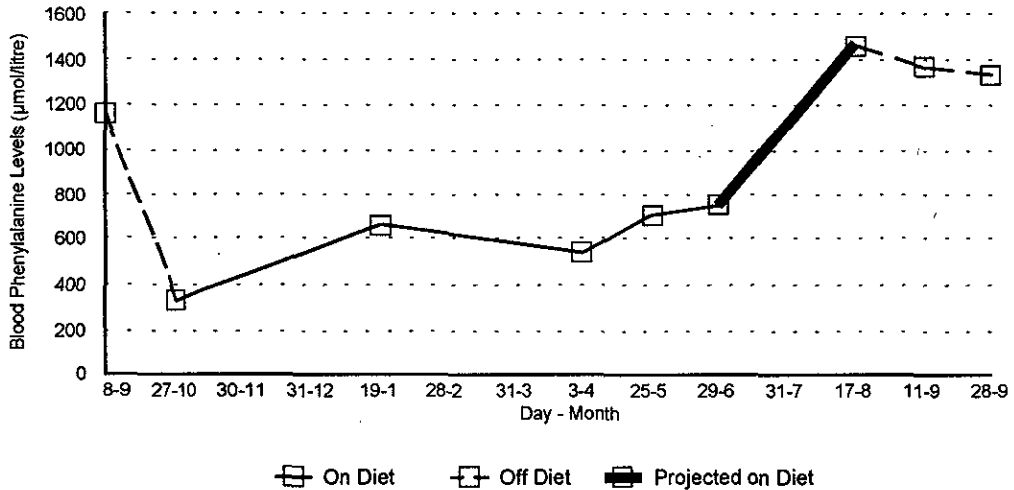
### *Procedures*

A phenylalanine-restricted diet had been prepared for VW by the dietitian and it was known that VW received a special diet during her childhood but there had been a number of occasions during early adulthood when that diet had been modified or ceased. This had

been governed largely by the recommendations of available clinical literature about PKU at that time. However, during the 13 months period of the study, there had been only two periods when she did not receive the special diet; the first occasion preceded the study but recordings of blood assays taken at that time show that she was not receiving the diet during September 1992; the second occasion was an agreed period during August and September when assays were taken at three intervals. (FIGURE 1 shows diet status and blood assay results during the period of the study.)

At the beginning of the study baseline recordings of VW's behaviour were made by the clinical psychologist in order to establish her repertoire of responses. Accurate charts were then designed and used to record descriptions and frequencies of the observed behaviour throughout the study. An interval sampling method was combined with a recording of descriptive observations taken at one minute intervals over 0.5 - 1.0 hour periods on frequent occasions throughout the week. Observations were made in a variety of settings (e.g. mealtimes, recreation and relaxation) whilst sitting as discretely as possible in the same corner of the room on each occasion. A summary of the frequency data was then made for two periods, i.e. when VW was 'on' or 'off' the special diet. This was then matched with the regular blood assays to determine whether or not the special diet had been effective in maintaining an acceptable level of behaviour.

**FIGURE 1**  
**Diet Status and Blood Phenylalanine Levels**



All other medication was reviewed and carefully withdrawn by the medical specialist at the start of the study. Regular drug reviews and study reviews were also conducted during this period. In addition, nursing staff kept records of menstruation cycles and sleep patterns in case either of these states affected observed behaviour.

## Results

A summary of results of both baseline observations of behaviour (i.e. those recorded when VW was 'off' the special diet and of observations when VW was 'on' the diet) have been included in TABLES I and II.

From TABLE I, results indicate that most observed behaviours were more frequent whilst adhering to the phenylalanine-restricted diet. The notable exceptions to this were the following (No. 1, 2b, 6, 8b): sits quietly still (29.4% during baseline and 10.5% whilst on the diet); looks towards an object (11.7% versus 2.9%); teeth grinding (3.9% versus 3.4%); and smiles (0.7% during both baseline and intervention).

TABLE II portrays a similar picture where the mean behaviours per 30 minute period of observation have been presented. In addition, observed behaviours 2c and 8b appear lower whilst on the diet. These were: looks downwards, and smiles, respectively.

**TABLE I**  
**Percentage Frequencies of Total Behaviour Observed for VW**

Observed Behaviour	% Freq. of Total Behaviour Observed	
	BASELINE (off diet)	INTERVENTION (on diet)
1. Sits quietly still	29.4	10.5
2. Looks towards		
a) others	6.7	9.1
b) object	11.7	2.9
c) downwards	22.8	25.2
3. Leaves seat	1.7	4.2
4. Stereotyped movements: rocks in chair, both hands held together resting on lap	13.3	27.0
5. Starts to strip	0.1	1.7
6. Teeth grinding	3.9	3.4
7. Throws object	0.0	1.0
8. a) Frowns	0.7	2.0
b) Smiles	0.7	0.7
9. Outstretches one arm to object	1.3	2.0
10. Interaction by staff	1.9	2.9
11. Other behaviour (if feeding, then 1-10 recorded for this activity)	5.8	7.4
TOTALS	100.0	100.0

If some of the observations are grouped together, for example, those considered by the nursing staff to be particularly disruptive or unsociable/aggressive (such as 4, 5 and 6), then the following percentages are found: 17.3% (baseline) and 32.1% (intervention). An examination of the woman's diet status and blood phenylalanine levels (FIGURE 1) revealed that this higher percentage frequency of observed behaviours (4, 5 and 6) occurred whilst on the diet when her blood phenylalanine levels were lowest (325-750 micromol per litre).

## Discussion

On analysis of the recordings made of the various observed behaviours, it would seem that most behaviours reduced in frequency whilst the woman was off the special diet. In particular, it was noted that the woman sat quietly still for longer periods of time but that teeth grinding was slightly increased and stereotyped movements decreased. Although little had changed in her daily routines and activities, her 'other' observed behaviours (No. 11 in TABLES I

**TABLE II**  
**Percentage Behaviour per 30 mins Period of Observation**

Observed Behaviour	% Behaviour per 30 min. Observation	
	BASELINE (off diet)	INTERVENTION (on diet)
1. Sits quietly still	18.7	5.4
2. Looks towards a) others b) object c) downwards	4.3 7.5 14.5	4.6 1.5 12.9
3. Leaves seat	1.1	2.1
4. Stereotyped movements: rocks in chair, both hands held together resting on lap	8.5	13.8
5. Starts to strip	0.1	0.9
6. Teeth grinding	2.5	1.7
7. Throws object	0.0	0.5
8. a) Frowns b) Smiles	0.5 0.5	1.0 0.4
9. Outstretches one arm to object	0.8	1.0
10. Interaction by staff	1.2	1.5
11. Other behaviour (if feeding, then 1-10 recorded for this activity)	3.7	3.8

and II) had decreased. In addition, the group of observed behaviours, considered by the nursing staff to be disruptive or unsociable/aggressive also decreased when the woman was off the diet.

There are several possible conclusions of these results. The first is that the higher blood phenylalanine levels, corresponding to her baseline periods, may have resulted in a general increase in her lethargy and social withdrawal. Indeed, she sat still for more of the time and engaged less in anti-social behaviour. But it should also be noted that

staff generally interacted with her less whilst she was off the diet (perhaps because she was more withdrawn?). The second conclusion is that her being on the phenylalanine-restricted diet may have made her more frustrated at being "denied" subjectively more pleasant tasting foodstuffs and having to eat comparatively less volume and perhaps even less frequently. Indeed, seeing other people eat "ordinary" foods which might be more pleasant tasting and often in greater quantities (especially on the occasions of "second helpings" at lunchtimes), may have resulted in the

woman behaving aggressively or unsociably towards others (e.g. stealing others' food, stripping and throwing objects). Given that other variables, such as medication, menstrual period and sleep patterns were also monitored and did not appear to have been particularly unusual or abnormal, these conclusions seem plausible.

However, matching these results to those of other studies is interesting. On the one hand, it has been argued that quality of life measures and behavioural abnormalities seem to decrease in treated phenylketonurics (Pitt, 1971) who have to adhere to a strict diet; on the other hand, intellectual functioning and performance on executive tasks deteriorates whilst off the special diet. There also seems to be growing evidence to suggest certain neurological deficits are apparent in greater concentrations of phenylalanine in the blood. Using additional data, it would have been useful to compare behaviour directly with blood phenylalanine levels during the diet periods to see how closely these levels correlate to behavioural changes, especially since the 27-10-93 value is half that of the 29-6-93. Likewise, a comparison of behavioural changes just before going on the diet and just after coming off the diet would also have been interesting to investigate further, perhaps in a future study.

It would seem that treating phenylketonurics is especially complicated when the special products available that are free from phenylalanine taste less desirable (Thompson, 1993) and are sometimes rather unpalatable

(author's experience!). It is also difficult to convey an explanation to a person whose intellectual development has been affected by the presence of the disorder. Therefore, it is a compromise situation that must be adopted: to achieve acceptable safe blood phenylalanine levels so as not to sufficiently reduce quality of life by becoming withdrawn and lethargic, but also not to sufficiently deprive the person from enjoying pleasant tasting foods that, in careful quantities, may not adversely affect the neuropsychological status of the person. It is suggested that "acceptable" blood phenylalanine levels may be in the range 1000-1200  $\mu\text{mol/l}$ ; and a "modified" diet to achieve this might consist of the following:

1. Puddings (such as rice pudding) replaced by desserts that are free from milk e.g. sponges;
2. Powdered milk used in cereals, custards and yoghurts;
3. "Coffee Mate" used in drinks (such as coffee/tea);
4. Use of a phenylalanine-free, amino acid, vitamin and mineral supplement;
5. Blood phenylalanine levels monitored at monthly levels;
6. Observations of behaviour conducted at frequent intervals.

Finally, it is suggested that a team decision should be made that combines the ideas, knowledge and expertise of different professions such as dietetics, clinical psychology, nursing and psychiatry. Consent, and where possible,

involvement in decisions should also be explored with relatives at each stage of the diet review.

## Summary

A 39 year old woman with a childhood diagnosis of phenylketonuria was observed over a 13 months period. Interval sampling of her behaviour in a variety of settings was recorded together with descriptive data. Blood phenylalanine levels taken at regular intervals and known dietary status revealed that the woman had a greater incidence of disruptive or unsociable/aggressive behaviour during periods of lower blood phenylalanine levels. These results reflected the periods of adherence to the phenylalanine-restricted diet.

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