

Welcome to
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Programme Information & Abstracts

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✚ N S P K U ✚

The National Society for Phenylketonuria (United Kingdom) Ltd.

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The work of my father, Dr Asbjorn Folling

By Ragna Folling Elgjo

Almost 70 years ago a mother went to a doctor asking for help with her two disabled children aged 4 and 7 years. They had looked well and healthy at birth, but both gradually changed into helpless beings, both physically and mentally. Other doctors had not been able to help, but the mother never gave up the hope that something could be done. This last doctor was Asbjørn Følling, and he was my father. He managed to describe the disorder as an entity and the aetiology was partly elucidated. This was the first of the inherited diseases of metabolism where a connection between a biochemical disorder and mental deficiency was described. It is now, as a shortening, called PKU. This gave hope of further possibilities to find treatments which we now have seen working. The biochemical background of his work was published in a German journal and the clinical entity in a Nordic medical journal in 1934. Little attention was given to the work until some years after the Second World War.

I will tell a little about his background, his education and work, how the discovery was made, and also about his personality, as this was probably crucial to the discovery at that time. So my talk will probably be more personal than many of the more scientific medical ones, and easier for the younger part of the audience to follow.

He was born on a farm in the middle of Norway. Already as a little boy he was considered to be a part of the working team, like all the other children on a farm were in those days. I will tell a little about how life was at that time, and his difficulties in being able to become a student, as he preferred reading to farming. He became a biochemical engineer and then a medical doctor. Later he got a scholarship in America where he studied endocrinology and changes in the metabolism of Marathon runners at high altitudes for some time.

Back home in Norway he was appointed as head of the University Nutritional clinic, and later to establish new laboratories in the Veterinary College. In this time he met the two PKU children for the first time. I'll go back to tell about his detailed work with the urine samples from the two children, how he concentrated and purified the specimen that gave the urine a special odour, and how he identified it. Later he co-operated with others to prove that the disease was recessively inherited. He was concerned about the possibility to trace the carriers of the gene and also to find a diet free from phenylalanine in order to avoid damage of the brain.

At the end of the talk I want to tell more about my father's personality with a few characteristic stories about him.

Thirty Years' Experience of the Management of Phenylketonuria

Dr Campbell Davidson,
Consultant Paediatrician
Alder Hey Children's Hospital
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This presentation is not a comprehensive view of phenylketonuria (PKU) but is based upon anecdote and clinical experience over the last 30 years and represents personal practice and views. The practices outlined are not the only ways of managing PKU.

There are many basic questions which remain unanswered and need to be addressed. Evidence based practice on broad questions of treatment are unethical and unacceptable in PKU and personal experience in practice should not be ignored.

My initial introduction to PKU was as a medical student in 1966 before national screening. My impression of these patients was their variability and clinical appearance and outcome. Over the years I would conclude that optimal outcome today depends on early diagnosis, good control and ideally life long and careful adherence to a monitored diet.

The diet remains the bedrock of treatment but other novel treatments may offer alternative ways of managing PKU. Monitoring of levels at home and by regular attendance at PKU clinic maintains contact but families need to know that perfect phenylalanine levels every time is exceptional.

Many dietary and nutritional issues have arisen over 30 years. Those covered have been selected because of personal experience and topics include; aspartame, selenium deficiency, vitamin B12 deficiency, feeding issues, compliance, breast feeding, gastrostomy feeding and diet for life.

There have been recent advances in PKU and these include magnetic resonance imaging and genotyping. Do we need to know about these

and is the information helpful with patient management?

Finally, maternal PKU, first described by Dent in 1957 is a growing area of treatment. Our experiences in Liverpool are given including time of commencement of diet and outcomes of pregnancies.

I have learned much about PKU over the last 30 years but there are huge gaps in our knowledge which we must remedy and specifically address the issue of dietary needs, compliance and rationalise the question of life long treatment.

Bone Mineral Status & Phenylketonuria

Dr N.J. Shaw

Consultant Paediatric Endocrinologist

Birmingham Children's Hospital

The accretion of bone mineral during childhood and adolescence is critical in the achievement of peak bone mass which it is now recognised is obtained by the end of the second decade of life. As peak bone mass is felt to be a significant determinant of the risk of osteoporosis in adulthood, factors in childhood and adolescence which may affect this are of considerable interest. Although 70-80% of peak bone mass is genetically determined important environmental influences include nutritional intake, exercise and puberty each of which may be compromised by chronic childhood disease.

The assessment of bone density in children with chronic disease has produced a large body of research in the past decade. This has been facilitated by the availability of simple non-invasive methods of measurement. Single photon absorptiometry (SPA) has been available for over 20 years and uses an Iodine 125 source to scan the predominantly cortical bone of the peripheral skeleton at the forearm producing a measurement of bone mineral content (gm/cm). This has now been largely superseded by X-ray based methods such as dual energy X-ray absorptiometry (DXA) which have the ability to measure the predominantly trabecular high turnover bone present in the spine and hip. It is currently the most favoured technique as it is rapid (1-2 minutes on current scanners), has a high accuracy and precision and uses a low radiation dose. It produces a measurement of the bone mineral density (gm/cm²). However an often overlooked problem with this method in growing children is that the measurements are influenced by body size. As results are usually reported in relation to that expected for a child's age this means that a small short child will have a lower bone density than an average size child of the same age merely as an artifact of the measurement method. It is therefore important that such results are compared with that expected for a child of similar body size. An additional technique that has been used in some paediatric studies is quantitative computed tomography (QCT)

which has the ability to separately measure trabecular and cortical bone. It is the only technique to measure true bone density (gm/cm³) and therefore its results are not dependant on body size. Its disadvantage however is a considerable radiation dose. A recent development of this technique is pQCT which measures bone in the peripheral skeleton such as the forearm or femur and has a significantly lower radiation dose.

There have been several studies which have examined bone density in children and adults with phenylketonuria using a variety of techniques. QCT of the lumbar spine in 11 adults showed reduced bone density with standard deviation scores for age (Z -scores) ranging from -0.6 to -3.3 with 4 patients having Z scores below -2.0. A study using SPA in 26 children showed a normal increase in bone mineral content until the age of eight years and a fall beyond that age. Poor dietary compliance with phenylalanine levels greater than 1200 umol/l was associated with reduced bone mineral content. Another study of 44 patients (age 6 - 29 yrs) using DXA of the lumbar spine showed Z scores of -1.0 to -2.5 in 32% with 14% having Z scores below -2.5. A negative correlation of bone density with the amount of casein hydrolysate mixture in the diet was seen which was not evident in those on an amino acid mixture. A fracture questionnaire of 85 patients age 0.3 to 33 years showed no overall difference from sibling controls. However analysis of those patients older than 8 years showed a 2.6 fold increase in fracture frequency. Two possible explanations for low bone density in phenylketonuria have been proposed. One is that poor dietary compliance causes a toxic effect of high phenylalanine levels on bone whilst the alternative hypothesis is that the artificial diet produces an inadequate mineral intake.

Thus a number of studies have suggested the presence of reduced bone density in individuals with phenylketonuria. However not all of these will have adequately corrected for short stature and the implications for future fracture risk in adulthood are currently unclear. At present there is little justification for routinely measuring bone density in children with phenylketonuria as no clear preventable factors have been identified. There is however a need to learn more about the aetiology and therefore possible means of prevention which indicates the need for further research.

Genetic Update

Dr Linda Tyfield,
Southmead Hospital,
Bristol

Most people's understanding of Phenylketonuria or PKU is in the biochemical definition: phenylketones in the urine and high levels of phenylalanine in the blood (hyperphenylalaninaemia). Those who are more closely involved with the disorder (dietitians, paediatricians, parents, and the affected individuals themselves) know now that there are different degrees of severity of the disorder. This requires greater refinement of the simple definition of what is meant by PKU.

Genetic analysis has provided some insight into why there are different degrees of severity of the condition. More than 400 different mutations have been described worldwide in the gene that is involved with PKU and although a few mutations are common, most are rare. Some are known to result in a more severe PKU whereas others are always associated with a mild form of the condition in which little dietary restriction of phenylalanine is required to maintain normal growth and development. Through mutation analysis it has been possible to trace the origins of the disease in different populations and to trace the migration of families through different geographical areas.

In this talk I will put 'genetic travel' into a perspective of space travel to illustrate the depths to which we go inside the human cell in order to study genetic material. I will describe some unusual mutations that we have characterised recently in the UK population and, time permitting, I will show how computer modelling is used to explore the effects of single base changes in the DNA.

Towards Self Management

By Carol Ferguson, Paediatric Dietitian, Newcastle upon Tyne.

The NSPKU is currently developing a Self Management Package for those with Phenylketonuria (PKU). The aim of the package is to help those with PKU to understand their condition and its management.

The package has been developed to fulfil a perceived need. During 2001/02 a questionnaire was used in three PKU Centres to find out the PKU knowledge of, and the practical involvement in management undertaken, by young people with Phenylketonuria between 7-15 years. The results of the questionnaire suggested that the majority of those questioned had gaps in their knowledge and self management skills. The Medical Advisory Panel of the NSPKU enlisted a number of dietitians to head up the Self Management project. They, in turn, drew on the knowledge and experience of many people including nursery nurses, teachers, adults and youngsters with Phenylketonuria to help develop enjoyable activities for 7-11 year olds. These could be used to deliver a variety of PKU messages.

The activities cover five subject areas: What is PKU?, Genetics, Blood Monitoring, Food and Diet and Coping with PKU.

Relevant activities to help understanding and build confidence in the self management of Phenylketonuria are now being trialled and will soon be available to PKU Centres throughout the United Kingdom.

We hope that they will enhance independence and self esteem amongst our 7-11 year old children with Phenylketonuria. The Working Group will now turn its attention to developing further activities on PKU topics suitable for other age groups.

Tetrahydrobiopterin: a new approach to treat PKU

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Exactly 50 years after Bickel and coworkers initiated dietary treatment by phenylalanine restriction clinicians and researchers worldwide are still searching for an alternative approach to the treatment of phenylketonuria (PKU). Today we know that maintaining the restricted diet is beneficial if not essential to prevent brain damage, but there are still disagreements as to how long this diet should be continued. A number of nutritional products with improved quality are available in most countries, but many adolescents and young adults generally do not comply with the recommendations for monitoring and control of phenylalanine concentrations, and two thirds of pregnant women in the United States did not follow the diet before becoming pregnant.

While still facing technical difficulties to replace the defective gene and/or enzyme, one new approach to treat at least some PKU patients seems to be a close reality. A relative high percentage of patients with mild PKU may benefit from substitution with tetrahydrobiopterin (BH₄) in that oral administration of the natural cofactor for phenylalanine hydroxylase (PAH) reduces their plasma phenylalanine levels (1). BH₄ can obviously activate the specific mutated PAH by either increasing the affinity for BH₄, by three-dimensional structure stabilization, or by its chaperone-like activity. It has been shown that a number of DNA mutations correlate with BH₄ responsiveness (2) and a number of patients with mild PKU or hyperphenylalaninemia are presently on BH₄ treatment without the low-phenylalanine diet (3). The main disadvantage of this approach is the relative high costs of BH₄ and so far the lack of regulations in some Societies. A BIOPKU database (www.bh4.org/biopku.html) provides an extensive information on BH₄-responsive HPA/PKU.

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Enzyme therapy for Phenylketonuria with Phenylalanine Ammonia Lyase as a potential new treatment option

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PKU responds to treatment with low phenylalanine (phe) diet. However, compliance is difficult; and if for life (as recommended), probably unrealistic. A new potential mode of treatment: involving enzyme substitution, to eliminate phenylalanine, with protected phenylalanine ammonia lyase (PAL) is currently being explored. PAL converts phe to the harmless by-products (*trans*-cinnamic acid and trace ammonia). Taken orally, PAL could deplete excess phe; the rationale is based on studies of exchange between compartments (Christensen et al., *Am. J. Physiol.*, 205:255; 1963). We have reported an efficient method to produce PAL enzyme and have shown its efficacy in the PKU mouse models in primary short-term pre-clinical drug administration trials (Sarkissian C.N. et al., *PNAS* 96: 2339-2344, 1999). We also have the first evidence that PAL treatment, administered outside the brain, reduces elevated brain phe levels that are associated with altered brain structure/function and impaired mental development. These findings further support the possibility for PAL treatment in PKU patients with primary phenylalanine hydroxylase deficiency.



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