

# Abstracts of the 25th Annual NSPKU Conference

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# **THE BIRTH OF NSPKU**

Brian Talbot

Secretary NSPKU 1974-1980,

Vice Chairman 1980-1982 & Chairman 1982-1984

Our son Paul was diagnosed a PKU a few days after he was born in 1971, his initial treatment and the lack of information resulted in a firm resolve to help form an association of parents – if ever the opportunity came.

It did, in mid 1973 when Sheila and I heard about Brian and Sylvia Smith of Runcorn as a result of a 'plug' on the Jimmy Young radio show and a small feature in the Daily Mirror. In September 1973 we took Paul along to the inaugural meeting in a humble community centre on a housing estate in Runcorn. With only eight adults and their children I was not hopeful! We were there five hours, talked a lot, and decided little. However we did agree to meeting again in November to try and arrange a weekend together early in 1974.

The November meeting in Manchester attracted 12 adults (better!). I agreed to be Secretary of the Steering Committee of the proposed National Society for Phenylketonuria and allied disorders. The talk this time centred on a weekend conference in 1974 which Brian Smith again took the lead in arranging.

Everyone involved advertised this weekend, as a result our 1st Annual Conference was held on the 1st weekend in March 1974, at the Progress Hotel in Blackpool – you cannot imagine anything more different from the Norbreck Castle!

Fourteen couples and 30 children, about half were PKU and four of these were variously mentally retarded due to late diagnosis.

The local branch of the Lions Club took care to the children with various degrees of success. We had a paediatrician to talk about PKU and Miss DEM Francis from Great Ormond Street Children's Hospital to talk about the diet. Miss Francis also became our main medial advisor. We never stopped talking (some of us continued until 3 am Sunday morning).

Five couples agreed to continue on the NSPKU Steering Committee our objectives for the next year were:

- increasing contact with the parents of the estimated 1600 PKUs in the UK;
- produce a newsletter;
- produce a leaflet for parents;
- gain registration as a charity;
- establish a medical advisory panel with the medical profession;
- fund raise.

The Steering Committee met four times in 1974 and made good progress with our aims.

1975 saw a much better 2nd Annual Conference at the Chadwick Hotel St Annes (definitely up-market). Similar pattern to the first but with the lessons learned. A Council of Management was properly elected – we had a distinct feeling we were being taken seriously by the medical profession – we were off!

# **DIAGNOSIS AND MANAGEMENT OF PHENYLKETONURIA: PAST, PRESENT AND FUTURE**

Isabel Smith

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## **The early years – 1934 to 1970**

As I am sure you all know PKU was discovered by a Norwegian biochemist called Folling in 1934. However it was a British geneticist, Penrose, who gave the condition its name and carried out a large scale screening program in handicapped adults. Around 3% proved to have PKU. It was also Penrose who first proposed the use of a diet low in phenylalanine and outlined how this could be prepared. This was taken up in the 1950s by a biochemist called Louis Woolf. He demonstrated the technique to Horst Bickel who then used it to treat the first patient in 1953.

In 1957 the UK infant welfare clinics, which had been established all over the country, adopted the Phenistix test on wet nappies as a test for PKU in infants between 3 and 6 weeks of age. At the same time a group based in the Oxford Region (Louis Woolf again) was developing a very good laboratory-based system for testing liquid urine which health visitors collected at the clinics. The Phenistix test proved an insensitive method of detecting PKU (50% of affected infants were missed) and was overtaken by Robert Guthrie's work on blood testing. In 1964, Scotland implemented a nation-wide program of routine neonatal testing using blood obtained from a heel prick. England, Wales and Northern Ireland followed in 1969/70.

The dietetic management of PKU was worked out step by step from the 1950s onwards. Many mistakes were made in the early years due to lack of knowledge and experience. Children did not always grow properly and some became anaemic and ill due to nutrient deficiency. The special products which were available were limited in scope and very unpalatable. Gradually, however, the paediatric dietitians developed their skills and the food companies improved

their products so that by the time routine screening was introduced it was possible to make a reasonably good job of management.

The problems in the offspring of women with PKU were identified in the 1950s and 1960s although there were no attempts at treatment in pregnancy until the 1970s. Malformations in different organs, especially the heart, low birth weights, slow growth after birth, development delay and long-term handicap were common problems. However, as the majority of women of fertile age were handicapped pregnancy was not a common event and the issue did not receive wide attention.

Despite the imperfections, the early program of screening and treatment for PKU in the UK laid the foundation for development of many of the specialist laboratories and clinics for the management of children with metabolic disease existing today. In the UK we have a well organised and equitable system for the screening, diagnosis and management of PKU and, dare I say it (?), the oldest and best lay society. Congratulations!

### **How did knowledge change – 1970 to 1994**

From the beginning it was obvious to paediatricians who looked after children with PKU that early treatment prevented mental handicap – they saw the families with a severely handicapped older child and a younger one treated from early infancy who was developing normally. Not everyone believed it initially but by the early 1970s all the arguments about whether or not screening was justified faded away. It was clear that mental handicap due to PKU had disappeared in the screened population and it was recognised that screening was actually cost-saving as well and cost-effective.

Screening and early dietary treatment could truly be said to be one of the great advances of modern medicine. However, in the battle to secure the funding for screening adherents played down some of the problems with treatment. They argued passionately that early diagnosis and treatment was straight forward and resulted in entirely normal outcome although, some parents were reporting subtle problems with reading, arithmetic and behaviour. The diet, then as now, is a difficult form of therapy with potential dangers as well as benefits. Compared with nature's way of controlling blood

phenylalanine levels it is a relatively blunt instrument and phenylalanine control can be hard to achieve especially in biochemically severe forms of the disorder. There were also major uncertainties about how strict treatment should be and how long it should continue. From the mid 1970s onwards, with the battle for screening won, there was a gradual re-appraisal of some of the finer points in the PKU story.

### ***How long should treatment continue?***

There had been reports from the US that it was safe to stop treatment at four to six years of age. In 1974 a paediatrician in Poland, Barbara Cabalska, reported her observations on children with PKU detected by screening and treated to age four. She found that intellectual ability was not as good after withdrawal of treatment. A report from the UK in 1978 showed that children who stopped the diet at eight years also showed a fall in ability though less than in the Polish children. In 1981 a study from the US reported a relative decline in ability and scholastic achievements in children who had stopped treatment at age six. Although these effects were relatively subtle, from then on paediatricians advised continuation of the diet at least into the teens.

In addition to worries about general ability, there were a few reports in the 1960s and 1970s of worrying symptoms developing in a few late treated subjects after withdrawal of treatment, that is difficulties walking and controlling movement. These features were characteristic of damage to the motor pathways of the nervous system. By the 1980s there were also reports of minor changes in control of movement which could be detected at medical examination in otherwise healthy subjects who had been treated early but were now on a normal diet. Then, most worrying of all, a small number of early treated subjects were reported to have developed the difficulties of walking and controlling movement which had previously been described in late treated subjects.

By now paediatricians and adult physicians were advising their patients to continue treatment into adulthood, provided this was practical and could be carried out safely. This change in practice was supported by other new findings. Elevated blood phenylalanine levels had long been known to cause dynamic, biochemical changes

in some of the chemical messengers of the nervous system (dopamine and serotonin) in proportion to the phenylalanine rise. Psychologists began to ask whether these changes had any effects on function. Clearly any effects would be subtle, would vary from one individual to another and would probably be difficult to measure since most subjects receiving a normal diet are perfectly healthy and leading a normal life.

A number of research groups have found that the performance of certain defined tasks, dependent on short term memory, concentration and assembly of information, changes in response to blood phenylalanine levels. These are not characteristics which are easily observed in daily life (certainly not by doctors sitting in out-patients!). The significance of these observations is still debated but the findings are not inconsistent with the observations of parents, who will sometimes report that they know from their child's behaviour when levels rise and, patients returning to dietary treatment may comment on their improved ability to concentrate and organise their lives. Observations in the handicapped population also suggest that returning to dietary treatment benefits behaviour.

Alongside these clinical and psychological observations came the first reports of changes in the brain scans of children and adults whose blood phenylalanine concentrations were greater than  $600\mu\text{mol/l}$ . The fatty insulation in the brain (the myelin) develops a higher water content in response to raised phenylalanine levels. The extent of the change is proportional to the rise in phenylalanine. Whether the changes are significant in real life is not known but clearly cannot be ignored in our thinking about policies on dietary treatment for PKU.

### ***How strictly should blood phenylalanine be controlled?***

Until the late 1980s many paediatricians regarded blood phenylalanine levels of around  $600\mu\text{mol/l}$  as entirely acceptable for the management of PKU, even in infancy. Because the effects of moderately raised phenylalanine levels are subtle and slow to develop and vary from subject to subject, it took a long time to demonstrate that there was clear relation between intellectual ability and quality of phenylalanine control during treatment. Our national

register made an important contribution here by providing the large number of subjects needed for this kind of study. By the early 1990s there was general agreement that stricter control of phenylalanine in the first half of childhood was necessary to achieve optimal intellectual function in PKU although later on a more relaxed approach was acceptable.

### ***What about pregnancy in women with PKU?***

By the late 1980s a lot had been learned about the factors influencing the outcome of pregnancy in women with PKU. Again blood phenylalanine control emerged as a key factor in preventing the effects of maternal PKU on the fetus. When average blood phenylalanine levels are below 600-700 $\mu$ mol/l in early weeks of pregnancy, congenital anomalies are rare, although stricter control is needed to achieve optimal fetal growth and development.

### ***The molecular genetics –PKU is a highly varied condition***

Paediatricians and dietitians working a lot on PKU had known from early on that there were big differences between patients with respect to their blood phenylalanine levels at diagnosis, the smoothness of their phenylalanine control during treatment and the amount of natural food which they could tolerate whilst on the diet. What is more, there were not discrete groups, but a wide and continuous spectrum of variation extending from individuals with phenylalanine levels just above the range occurring in carriers for PKU to those with levels 30 or 40 times normal.

Work on the genes which give rise to PKU has explained this variation – there are over 350 known mutations causing PKU with more still being described. This means that most parents of children with PKU, unless they are related, carry different mutations. Broadly speaking there is a clear relation between the predicted effect of the underlying mutation on the ability of the liver cell to break down phenylalanine and the biochemical findings in the individual concerned – the less the predicted liver activity the more severe are the biochemical features. Within families analysis of the molecular genetics can be used to identify likely carriers for PKU and to identify affected pregnancies. However, with so many different mutations exhaustive testing in the general population to see who are the carriers for PKU (for example, if an adult with PKU wants to know whether their partner is a carrier) is technically difficult.

## The present

The present I do not really need to tell you about and you will recognise, in the account set out above, the issues which have influenced those who look after your family. However, I will summarise the key elements of my own practice as a paediatrician with a special interest in PKU.

- A decision on treatment is made on the basis of quantitative measurement of blood phenylalanine and tyrosine interpreted in the light of current feeding.
- If blood phenylalanine levels are  $400\mu\text{mol/l}$  or above in the period immediately after birth and the phenylalanine/tyrosine ratio is greater than 4, treatment is started as soon as the diagnosis is made; services strive to achieve this by three weeks of age.
- Even if not treated any child who has blood phenylalanine levels above  $180\mu\text{mol/l}$  is monitored until fully established on three meals a day and a full mixed diet. A diet is introduced in these milder forms of PKU if levels rise to persistently above  $400\mu\text{mol/l}$  in the first two years.
- The aim of treatment is to control blood phenylalanine levels between  $120$  and  $350\mu\text{mol/l}$  as measured in a non-fasting blood specimen, where necessary allowing an upper limit of  $480\mu\text{mol/l}$  by school age.
- An upper limit of  $720\mu\text{mol/l}$  is chosen from the later years of childhood onwards.
- The issues concerning the decisions about long-term treatment are fully explained from an early age stage and revisited several times before the end of childhood. Every effort is made to pass on skills to the children and to encourage independence. The intention is that the decisions about treatment should ultimately be taken by the individual themselves rather than by parents, paediatrician or dietitian.
- The importance of dietary management for pregnancy are discussed with children early and are revisited several times.

## **The future**

The crystal ball is not a reliable research tool but I am going to risk my reputation with some predictions for the next 20 years!

Analysis of the molecular genetics of PKU will come to be used as a means of predicting the severity of the disease after diagnosis, and for detection of carriers amongst the partners of subjects with PKU, but will not provide us a “cure” for PKU.

Phenylalanine-free amino acids will be spun into a protein which can be used to manufacture better tasting textured substitutes for meat, fish and flour.

The specially manufactured foods low in phenylalanine will also be improved so that minerals and vitamins are more evenly spread. For example there will be calcium, phosphate and B vitamins in phenylalanine-low bread just as there is in ordinary bread and it will not be necessary to take these supplements separately.

Our neurochemist colleagues will uncover the mechanisms of neurological damage in PKU and enable us to make better judgments about whether there are likely to be any really useful therapeutic alternatives to controlling blood phenylalanine levels – I suspect the answer will be no but they may help us to do it better.

I need make no predictions about the work on an enzyme (phenylalanine ammonia lyase) designed to be taken by mouth in an attempt to reduce the need for dietary restriction of phenylalanine – I think we shall be hearing about the results of this work quite soon. Suffice it to say that I shall be delighted but surprised if we find ourselves able to dispense with the low phenylalanine diet.

# **ORAL HEALTH FOR LIFE**

Sally Craig

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A long standing interest in dental care for children with metabolic disorders began when times were less frantic in the Health Service and I was regularly able to attend a local clinic with a charismatic physician and his large group of patients, many of whom had Phenylketonuria (PKU).

On learning details of the diet, with sugary foods being allowed freely, I realised that special care was needed to lower the potentially harmful effect of such a diet on the teeth. From this I was asked to write a leaflet on dental health for children with PKU and their parents. This proved to be a challenge as the ideal dental advice is not possible because of the special nature of the diet. Dieticians throughout the UK were asked for comment and different ideas resulted in a flow of faxes to and fro before the final draft was eventually agreed and the advice sheets published. They have been very well received and Bristles is already regarded with affection.

This talk will discuss in more detail the common dental diseases and how they may be prevented with special reference to children with PKU. If prevention fails some treatments will be discussed.

Dental decay (the commonest dental disease in children) has become less prevalent over the last twenty years but with a noticeable slow down in improvements over the last ten years. In 1993 45% of 5 year olds were still affected by the disease and 40% had some untreated decay (O'Brien, 1994). Recent figures have shown worrying signs of an upward trend among the under fives, especially the underprivileged.

Loss of teeth in the young may result in impaired masticatory function, lowered self – esteem due to poor appearance, loss of space for the succeeding permanent teeth allowing teeth to be misplaced. If extractions are required in a child a general anaesthetic may be necessary and this is both unpleasant and not

without risk. In England in 1992/93 over 260,00 general anaesthetics were given to patients under the age of 18 years for tooth extractions.

Erosion is a problem that is being diagnosed more and this is a loss of tooth tissue due to attack by acidic substances in the mouth. Around one-quarter of 11 year olds currently have some degree of erosion, if only mild. The increase in the drinking of carbonated drinks has been implicated and this is of special relevance for children with PKU.

Each age brings its own particular challenges on the dental front and the talk will explore these from the very young child with erupting teeth through the years of the mixed dentition until finally all the permanent units are present. Throughout there will be special reference to the different dietary challenges to the teeth that the diet presents and how these may be minimised.

# **GENE THERAPY FOR PKU – WHERE ARE WE NOW?**

Linda Tyfield, Head of Molecular Genetics  
Southmead Hospital, Bristol

Gene therapy is the delivery of genetic material to specific cell types of an organism to alter its physiology or function.

Three components are required for development of gene therapy:

- an expressible form of the gene
- a means of transferring the gene into appropriate cells
- an animal model for testing the effects of gene transfer

For PKU, all three components have been assembled: the PAH gene has been cloned; it has been incorporated into vectors to carry it into liver cells; the effects are being tested on a strain of PKU mice.

Although the initial responses in the mice are promising – the blood phenylalanine concentrations fall substantially after treatment – the effect is difficult to sustain. The natural immune responses of the animal come into play and this creates problems for maintaining the effects for the long term. Currently, effects of suppressing the immune system are being tested.

# **DIETARY INTERVENTION IN THE PREVIOUSLY UNTREATED ADULT PKU**

Rosemary Hoskins

Senior Dietitian

Horizon NHS Trust, Radlet Hertfordshire

The success story of universal screening for PKU and dietary treatment has benefited many but there are those born prior to the implementation of these advances who have had the misfortune to suffer the consequences of untreated PKU including learning difficulties and behavioural problems. Dietary trials are now being carried out on a small number of this group to see if changes can be made to improve their quality of life.

Our investigation began when a consultant at our hospital was concerned about a previously untreated 35 year old PKU resident with a Phenylalanine level of more than 1700  $\mu\text{mol/l}$  and severe behavioural and sleep problems. The resident had been an in-patient since she was eleven years old, she had been diagnosed with PKU at the age of two and put on a diet for a short while, but after very poor compliance, the diet was discontinued.

A literature search was carried out to find out if other workers had reported any success with dietary intervention in this type of client. There were a few reports on a small number of cases, which was enough evidence for us to start dietary intervention.

An initial six week period of detailed assessment was made prior to the introduction of the Phenylalanine restricted diet with amino-acid supplement. The residents behaviour was monitored for a further 12 weeks on the diet. The results demonstrated a significant reduction of behavioural disturbances, accompanied by an improvement in the quality of life when blood phenylalanine levels fell below 700  $\mu\text{mol/l}$ .

Since our first study we have extended our work to include seven more adult untreated PKU's (two male and five female) in the age range 32 – 55 years, each with Phenylalanine levels of more than 1700  $\mu\text{mol/l}$  and all with varying degrees of behavioural

disturbance, one having severe eczema and asthma, and others with milder skin conditions. In total, six have shown improvements and two exhibited no improvement and have been taken off the diet.

We can conclude the following from these early studies:

- there is a reduction in behavioural problems
- there can be improvements in eczema and other skin conditions
- the residents are generally more manageable and more responsive
- their quality of life is greatly improved, as is that of the carers and the family

Improvements occur with blood Phenylalanine levels below 700  $\mu\text{mol/l}$  although it is difficult to predict at the outset who will benefit and who will not.

In October 1997, I arranged a meeting of dietitians and others working in the same field across the UK and Eire to share experiences. There was general agreement that the work to date indicates that there is a definite benefit to most untreated PKU's and that further studies are needed.

# **A REVIEW OF THE DIETARY MANAGEMENT OF PHENYLKETONURIA 1951 – 1992**

Christine Clothier – Dietitian Formerly Royal Liverpool  
Children's Hospital, Alder Hey

A brief review of the dietary management of phenylketonuria, from its inception by Doctor Horst Bickel in 1951 to the present day, illustrated with personal experiences and observations.

The original casein hydrolysate was extremely expensive, very difficult to prepare and so unpalatable that many patients had to be tube fed. Early diet sheets show that the treatment offered required an extreme degree of accuracy and until the late 1960's, all food had to be measured. In 1965 only two products were available on prescription 'Wheatstarch' and 'Aminex Rusks'. Mothers had to bake their own bread and it was the dietitian's job to teach them. 'Foods allowed freely', consisted of a meagre list of thirty three items, mainly condiments, flavourings, and fillers and strengtheners used in the baking trade. Diet sheets were complicated and confusing.

Gradually dietary management improved. More and more special products were produced and made available on prescription, starting with tinned bread in 1969. The government's recommendation in 1974, to reduce the high solute content of infant feeds, proved to be particularly beneficial for infants with phenylketonuria and in 1978 the new edition of McCance and Widdowson enabled the list of suitable foods for the treatment of phenylketonuria to be greatly extended. In the 1980's a range of protein substitutes were introduced, with a reduced odour and flavour, which proved to be more tolerable and less nauseating and by the 1990's the number of special products available, both on and off prescription, filled three or four pages of foolscap, when listed.

In reality, however, the difficulties of dietary management, present from the start, remain. The criteria for treatment, for the less academic, are complicated and many parents find them confusing, even baffling. An unpalatable, unpleasant smelling protein substitute has to be administered to a reluctant child who is denied

the right of enjoying attractive, appetising and most importantly 'normal' food. Palatable meals have to be constructed from 'special', often difficult to handle, unconventional ingredients. In addition there must be strict adherence to diet because of the ever present threat of mental retardation. Such stresses inevitably cause inadequate dietary control, disturbed behaviour and anxieties and tension in the family.



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