European Society for Phenylketonuria
- E.S.PKU -

The three landmarks of phenylketonuria

E.S.PKU:
A society that works to prevent handicap

Preface

The "European Society for Phenylketonuria" commemorates in 2004 to the three landmarks of phenylketonuria:

First landmark 1934: Prof. Dr. Ivar Asbjørn Følling discovered an until then unknown disease and identified it as "an inborn error" in the metabolism of the amino acid phenylalanine, leading to mental retardation, later on called "phenylketonuria".

Second landmark 1954: Prof. Dr. Horst Bickel published for the first time the results of a treatment with a phenylalanine-restricted diet in a two-year old child with phenylketonuria, which improved "the patient's mental status" and caused "a fall in the level of phenylalanine in the blood and urine".

Third landmark 1963: Prof. Dr. Robert Guthrie published his bacterial inhibition assay test, which made it possible to detect phenylketonuria in the first days of life. This "newborn-screening program" has first been introduced in the United States, followed by many other countries in the world.

At the time of discovery and first treatment of phenylketonuria, relatively little basic scientific information, very poor equipment and almost no technology were available. The basis of the work done by those three pioneers was disciplined observation and clear reasoning with the firm belief, that according to Følling "what was not known could be known".

As sign of deep gratitude for their lifelong commitment against mental handicap the European Society for Phenylketonuria has appointed the three pioneers Følling, Bickel, and Guthrie as posthumous honorary members.

The three landmarks opened the way for the early detection and treatment as well as for the successful prevention of mental retardation in the children afflicted. However, even if the first treatment of phenylketonuria - since more or less 50 years usually abbreviated "PKU" - was five decades ago, the problems for PKU's are anything but solved.

The whole work of our society has still to be dedicated to the prevention of handicap. Despite some improvement in the last decade of the 20th Century, the essential aims still remain the same as at the time of establishment of our society in 1987:

- To undertake all activities that can support the aims of our society
- To stimulate scientific and medical research in PKU and in allied disorders
- To promote the educational and social welfare of PKU's and persons with allied disorders

In addition, a so far more or less unsolved problem is the comprehensive care for adolescent and adult PKU's. Furthermore, even nowadays, PKU's are not in all European Countries screened and treated according to the latest medical recommendations.

However, it should always be kept in mind, that PKU is one of the very few disorders in medicine, for which since 50 years a treatment on a sound scientific basis is known. Innumerable investigations all over the world have confirmed, that the treatment with a "PKU-diet" is safe and effective and prevents mental retardation. Therefore, it must be ensured, that all PKU's irrespective of their age and of geographical borders get the best possible treatment and quality of life. The continuing aim of our society is therefore the prevention of handicap.

Dr. Jean-Marie Criem
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The first landmark:

The discovery of phenylketonuria

Prof. Dr. Ivar Asbjørn Følling

August 23, 1888 - January 24, 1973

The discovery of phenylketonuria:
The story of a young couple, two retarded children, and a scientist

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It is now 70 years, since a Norwegian scientist discovered the cause of mental retardation in an until then unknown "inborn error of metabolism". But who was this physician and scientist and what was the story behind his discovery? The man, who made this possible, Ivar Asbjørn Følling, had a long and successful life as scientist and medical doctor.

A long way to a chair at Oslo University

Følling was born on August 23, 1888, in the middle of Norway near Steinkjer as the youngest child of a family with a farm and had an older brother and 3 older sisters. The family name "Følling" was the name of the farm, and he himself was named "Ivar Asbjørn". But the latter was the name by which he became known. He was growing up with relatives of several generations all living nearby. The summer was short and the winter hard and cold. The growing children had to help to run the farm. In later years, Følling sometimes told, that once a day his mother said to him: "Today, you are 5 years old". That was all what was made of his birthday.

Følling liked the cold winters since they permitted to him to go to the 1-room school about 2 miles away. Due to his diligence he was allowed to continue with his studies in Trondheim, where his oldest sister lived after she got married. About the time as he finished school, he got tuberculosis. The doctor sent him home with the remark that he might come back, if he should survive the next year. He survived and decided not to be a farmer, but to become a scientist. Følling had the clear aim to finish the new Technical College of Norway which recently had been opened in Trondheim. However, at first he had to overcome some difficulties with his family who later on became very proud of him. In Trondheim, he could finish his studies in chemistry in 1916.

But Følling did not have settling down in mind and decided to go to Oslo to study medicine. He was teaching chemistry at the Dental College to earn the livelihood for his studies at the Medical College of the University of Oslo. Even after he received his medical degree, he continued with research and teaching based on his former special training in chemistry.

In 1928, Følling was one of the first physicians in Norway, who came to the United States on a Rockefeller Foundation Fellowship and could study for one year under American medical researchers at several universities. Following an interruption in Norway, he returned in 1930 to work together with the Harvard biochemist and physiologist Dr. Lawrence Henderson, doing research in high-altitude physiology and studying marathon runners. Shortly after his second trip to the United States he got married with Guri Opsahl.

Finally, in 1934, he got a chair for physiology and biochemistry at the University of Oslo, where he could establish himself as teacher and researcher. There, he was contacted by a mother with 2 retarded children and there, in his laboratory, he should discover an "inborn error of metabolism".

A young couple with two retarded children

Harry and Borgny Egeland married in 1923 following the graduation of Harry at the Dental College of Oslo University. They had a little daughter, Liv, and the parents wondered, that she did not speak only one word, as she was nearly 3 years of age. They told doctors their concern, but got only empty promises. Three years after his sister, the son Dag was born. He seemed to be normal for a few months, but then he became frailer as his sister had been at

the same age. He remained mentally like an infant. The parents became increasingly aware that Liv and Dag had a strange odor in urine.
The parents were continuously and everywhere asking for help, and even after admission of the son to the University Hospital in Oslo, no explanation for the condition of the 2 children could be found. But Harry Egeland could remember, that he had at the Dental College taken a course in chemistry and that his former teacher Følling was doing research. Borgny knew that her sister saw him occasionally at the house of a relative. Indeed, Borgny's sister explained to him the desperate situation of the Egeland's and Følling politely offered to examine the urine of the 2 children.

The discovery of PKU

At first, Mrs.Egeland brought urine from her daughter to the laboratory of Følling at Oslo University. The routine urine tests known at that time were normal. Finally, he added to a small sample a few drops of an aqueous ferric chloride solution, which was used to detect ketones in urine. The reaction which followed had never been seen by Følling before: a dark green colour, that faded within a few minutes. It was obvious, that something unusual must be the reason.

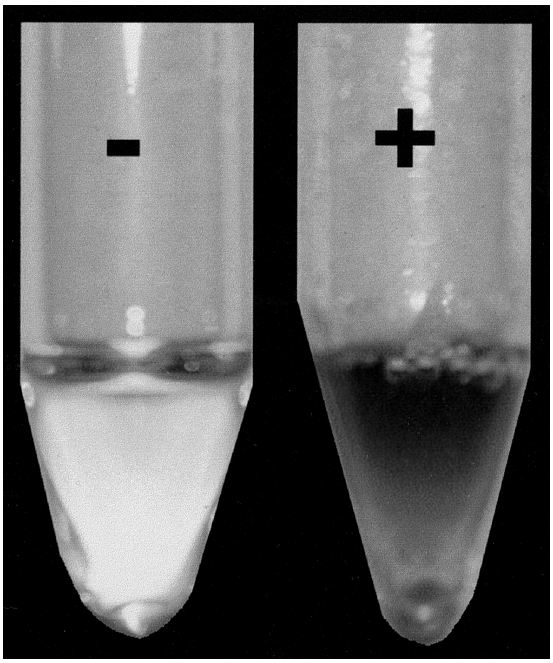

Fig.1:
An immediate dark green colour appears in the urine of untreated PKU's, which fades within a few minutes. This reaction, which does not occur in normal urine, led to the discovery of phenylketonuria.

Følling was now asking Mrs.Egeland to bring the urine of her son. And indeed, his urine gave the same reaction with the dark green colour, which never had been described in the scientific literature before.

For approximately 2 months, Mrs.Egeland brought every other day urine samples of her children to Følling's laboratory, "about 20 litres in all", as he recalled later. "Day after day, I worked to isolate the unknown substance". However, it turned out, that this was a difficult undertaking. In his publications in the scientific literature, he has later on in all details described, how he came to the conclusion, that the unknown substance in the urine samples of the 2 children was phenylpyruvic acid.

But the reason to find this substance was the question whether there was any connection between the excretion of phenylpyruvic acid and the mental retardation of the 2 Egeland children. Therefore, Følling was asking institutions, which took care for mentally retarded persons, to provide him with urine samples for further investigations. Among 430 children tested, he found 8 with the same abnormality as the Egeland's including 2 more sibling pairs.

Approximately 6 months after the first contact between Mrs.Egeland and Følling he published in the Norwegian and German scientific literature the results of his research and called the condition "imbecillitas phenylpyruvica" because of the mental retardation and the excretion of phenylpyruvic acid in urine.

The English geneticist Lionel Penrose called it "phenylketonuria", and in the late 1950s a lay-writer team in the United States used for the first time the abbreviation "PKU".
The discovery of PKU by Følling was a landmark, since it identified an "inborn error" in the biochemistry of an amino acid as cause of mental retardation. Later on, it became obvious, that this amino acid was phenylalanine.

Epilogue

Although the persistance of Harry and Borgny Egeland had finally led to the discovery of PKU, a treatment of their children came much too late for them. The little son died in 1936, whereas his sister Liv continued to live at the home of her parents. In later years, she had to be admitted into an institution near Oslo. The father Harry Egeland died with 46 years - a consequence of an extremely hard work, since he had to cover the costs for the medical care of his children by himself.

Only Mrs.Egeland survived her family and died in 1991 at the age of 87 years. At the 50th Anniversary Celebration of the discovery of PKU in 1984, the Norwegian Pediatric Society awarded her a special statue of a ferret depicting tenacity and determination. She died with the certainty, that the lives of her 2 children were not wasted, but that the discovery of PKU had helped innumerable families all over the world.

Følling continued with scientific investigations, not only on PKU, but also in many other fields of biochemistry. In 1953, he became the director for biochemistry and clinical chemistry of the Oslo University Hospital. There, he established a school for special technical occupations in medicine. Even after his retirement, he continued with some scientific work in his laboratory.

For his research and for the discovery of PKU, Følling received many honors, not only in Norway, but also in other European Countries and in the United States. President John F.Kennedy presented him in December 1962 an award, which symbolized Raphael, the Angle of Science, Healing, and Love - the life work of Følling.

Asbjørn Følling died on January 24, 1973, in his home in Oslo. His remains were interred in the church yard near the farm of his family.

References

Centerwall SA, Centerwall WR. The discovery of phenylketonuria. The story of a young couple, two retarded children, and a scientist. 2000. Pediatrics105: 89-103.

Følling A. Über Ausscheidung von Phenylbrenztraubensäure in den Harn als Stoffwechselanomalie in Verbindung mit Imbezillität. 1934. Z Physiol Chem 227: 169-176

Følling A. Excretion of phenylpyruvic acid in urine as a metabolic anomaly in connection with imbecility. 1934. Nord Med Tidskr 8: 1054-1059

Følling Elgjo, Ragna. The life work of my father Asbjørn Følling. Presentations at the 16th and at the 17th Annual E.S.PKU Meetings. 2002, October 5th, Oslo/Norway; 2003, October 31st, Hinckley, Leicestershire/United Kingdom.

The second landmark:

The first treatment of phenylketonuria
with a phenylalanine-restricted diet

Prof.Dr.Horst Bickel

June 28, 1918 - December 1, 2000

The first treatment of phenylketonuria: The story of the persistence of a mother, a small girl with PKU, and the commitment of a pediatrician

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Only 20 years after the discovery of PKU, a treatment of this inborn error of metabolism has for the first time been described. This is again a story of a persistent mother, a mentally retarded small girl and a committed pediatrician, Horst Bickel.

Schoolboy, medical student, medical doctor - on the way to Europe

Horst Bickel was born in Hamburg, Germany, on June 28, 1918, as son of a protestant vicar. He spent his childhood in Hamburg and attended - after moving to Berlin - the famous "Französische Gymnasium" (a French high school). After his examination, he studied medicine not only at the University of Berlin, but also in Lausanne/Switzerland, Freiburg/Germany, Innsbruck/Austria, Greifswald/Germany and in Vienna/Austria. There, he finished his studies and completed his Medical Doctor (M.D.) with a thesis about Addison Disease. This first part of his life set the direction for the subsequent career, opening his mind to wider perspectives in medicine and drawing him inevitably towards an international presence, that has left indelible results around the world.

But for a while, the second world war interrupted his plans for the future. He joined the German navy, where he worked as a doctor mainly on a ship for wounded soldiers. After the war, he could finally start the specialist training in pediatrics, first in the University Children's Hospital in Hamburg. However, again Bickel's studies were interrupted, this time due to tuberculosis. A friend of the family could arrange for him in 1946 a stay in a sanatorium in Davos/Switzerland. Because he had become fascinated with inborn errors of metabolism, Bickel moved to the service of Prof. Fanconi at the University Children's Hospital in Zurich/Switzerland. There, he pioneered the use of paper chromatography in pediatric research and described for the first time the "Bickel-Fanconi-Syndrome". The years between 1947 and 1949 in Zurich should become the most important for Bickel's later scientific work.

The first phenylalanine-restricted diet

The years from 1949 to 1954, Bickel could spent as research fellow at the University Children's Hospital in Birmingham/United Kingdom, under the wellknown pediatricians Sir Leonard Parsons and Professors Smellie and Squire. He continued with his special training in pediatrics, built up an amino acid and carbohydrate research unit and was in charge of a metabolic ward, in which he performed extensive studies on cystinosis and Wilson disease.

Already in Zurich, Bickel had looked for children with phenylketonuria, but futile. At the beginning of the fifties, a girl aged about 2 years was admitted to the metabolic ward, mentally severely retarded, unable to stand, walk or talk and without any interest in her food or surroundings. She spent her time crying and banging her head. Bickel could diagnose the disorder as phenylketonuria. The name of the little girl was Sheila Jones.

At that time, the cause of the mental retardation was completely unknown. It had been suggested, that it may be due to a secondary tyrosine deficiency. However, it had earlier been shown, that the addition of tyrosine to the diet did not lead to an improvement in the mental state. Therefore, it seemed, that the high level of phenylalanine and/or its metabolites may interfer with brain metabolism. The persistence of the mother, who was Bickel day by day asking for a treatment of her little daughter, finally led to the decision, to provide the girl with a phenylalanine-restricted diet.

Sheila Jones was the first child treated with a phenylalanine-restricted diet. Her behaviour before the treatment, her improvement under the diet and the deterioration with phenylalanine added to the diet has been demonstrated in a movie. Figure 2 is a reproduction from this movie.
Sheila was never able to understand what she has done for PKU's.

The difficulties, which Bickel and other members of the staff had to overcome, were manifold: A special casein hydrolysate had to be prepared, treated with charcoal to remove phenylalanine. Since tyrosine, tryptophane and cystine were going lost by this procedure, they had again to be added in suitable amounts. But a preliminary period of 4 weeks without any supply of phenylalanine had clearly indicated that small amounts of this amino acid are needed to prevent tissue breakdown. The addition of some milk was sufficient for normal weight gain and improved considerably the biochemical findings. Finally, the diet consisted of the hydrolysate, some milk, vegetables and fruits and a low-protein bread.

During this continued treatment a gradual improvement could be observed: Sheila learnt to crawl, to stand and to climb on chairs. She did no longer bang her head and stopped to cry continuously. It had, however, to be proved, whether the clinical improvement was really the result of the diet rather than a natural development. Without the mother's knowledge, 5 g phenylalanine per day were added to the hydrolysate. Within a short time, a definite deterioration occured: Sheila began to cry and to bang her head as before treatment and could within only one day no longer stand. She became irritable and lost again interest in her food as in the past. Bickel came to the final conclusion, that high levels of phenylalanine and/or its metabolites disturb cerebral functions and may possibly give rise to the mental retardation found in phenylketonuria.

The dietary treatment of phenylketonuria with a phenylalanine-restricted diet - in close collaboration with Prof.J. Gerrard, and Drs. E.Hickmans and L.Woolf - was a landmark in inborn errors of metabolism, also leading to the treatment of other disorders. Due to this research, Bickel became internationally known within a short time. In 1954, he returned to Germany to the University Children's Hospital in Marburg. In 1955, he obtained his postdoctoral qualification with a thesis on "Aminoaciduria in Childhood" and became in 1961 an associate professor of pediatrics - altogether many years loaded with work as assistent medical director at this university. In Marburg, he also started the first European Screening programme for PKU with the "Guthrie-test" and introduced the treatment with the phenylalanine-restricted diet.

A tremendously exciting challenge in troubled times

In 1967, Bickel was appointed Chairman and Director of the University Children's Hospital in Heidelberg. Its history is going back until the beginning of the 19th Century, when it had been established by the grand duchess Luise von Baden as one of the first hospitals in Germany

only for children. The position as director of this hospital was a challenge, since Bickel had some internationally well recognized predecessors. But the end of the sixties and the beginning of the seventies were the time of student riots. The students disturbed or blocked the lectures, asking for political discussions. However, Bickel was diplomatic and could overcome all difficulties very successful.

Despite the troubled times, the Metabolic Service under Bickel's personal charge became one of the world leaders in this field and the major centre for the study of metabolic diseases in Germany. He also worked hard to foster the development of many other services including the departments pediatric cardiology, endocrinology, neurology, neonatology and intensive care, oncology, and nephrology. As a result, during his tenure in Heidelberg, the Children's Hospital became a major international centre where many different specialities flourished.

Every one of the staff who had the privilege of working with Bickel, became fired by his enthusiasm. He encouraged them to develop their own interests and helped to foster their careers. In addition, he attracted many doctors from other countries, to work in the laboratories and on the wards. Such international collaboration was routine and mandatory. Without it, the German collaboration in the International Maternal PKU Study and the German Collaborative PKU Study would never have been possible.

Bickel was a member of many pediatric societies, for example Society for the Study of Inborn Errors of Metabolism, European Society for Pediatric Research, European Society for Pediatric Nephrology, German Pediatric Society, and German Internist Society. In 1972, he became an honorary member of the British Pediatric Association and in 1983, he was honored by being nominated as Fellow of the Royal College of Physicians (F.R.C.P.). Bickel was also a member of the editorial board of several national and international pediatric journals. For his pioneering work in the successful treatment of phenylketonuria, he received the "John Scott Award" from the City of Philadelphia. For many years, he served the German Pediatric Society as Vice-President and later as President.

Epilogue

After 20 years as Director of the University Children's Hospital in Heidelberg, Bickel retired in 1987. He had only a short time, to enjoy the summer home of his family on the Island of Rügen, which he finally could get back after the reunification of Germany. He loved the waterfront all his life. But even though he now lived far away and developed a severe illness, he participated in scientific meetings on metabolic disorders up to his last days. He always felt honored that a major award for research on inborn errors of metabolism had been named after him.

On December 1, 2000 the scientific and the metabolic community have lost an exceptional personality.

References

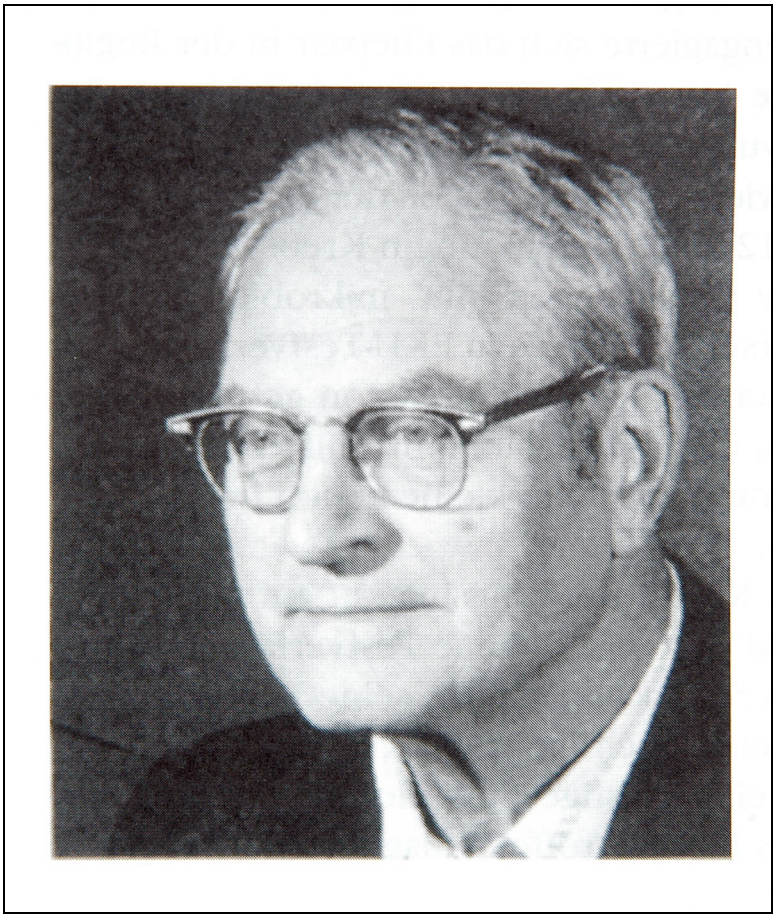
Bickel H, Gerrard J, Hickmans EM. The influence of phenylalanine intake on the chemistry and behaviour of a phenylketonuric child. 1954. Acta Paediatr. 43: 64-77.

Harms E. Horst Bickel, Pionier der Behandlung angeborener Stoffwechselstörungen. In: Wachtel U. Phenylketonurie. 2003. Stuttgart, New York; Schattauer, S.19-23

Hoffmann GF. In Memoriam: Univ.-Prof. Dr. Med. Dr. H.C. Horst Bickel, PhD, FRCP. 2001. J.Inher. Metab. Dis. 24: 611-613.

The third landmark:

Newborn screening on phenylketonuria



Prof.Dr.Robert Guthrie

June 28, 1916 - June 24, 1995

Newborn screening on phenylketonuria: The story of a father as scientist and a mentally retarded son

As has been shown in figure 1, PKU could be diagnosed by addition of a few drops of a ferric chloride solution to urine. This reaction, resulting in a dark green colour, has for many years been used to detect PKU as so-called "diaper test screening" in freshly wet diapers, introduced by Centerwall in mid of the fifties. However, this test procedure was for various reasons unsuitable for a large population of newborns. The scientist, who finally made the neonatal mass screening possible, was Robert Guthrie.

The career of the son of a travelling salesman

Robert Guthrie was born on June 28, 1916 in Marionville, Missouri, a small town in the Ozark Mountains. Bob, as he was called, had an older brother. The father worked as travelling salesman, mostly throughout Minnesota and Wisconsin, whereas the family moved to Nebraska and later to Minneapolis. There, Guthrie spent his school years. During vacations, he accompanied his father on selling trips and learnt a lot about making sales - a skill he later used in his campaigns to prevent mental retardation.

Guthrie had an active social life at high school, taking part in plays and assemblies. But he was not a consistent student and learnt mostly the subjects he liked. Following his graduation he wanted to go to university, but the 1930s were years of a deep economic depression. However, during the Roosevelt administration a special program permitted students to earn a small salary while studying at the University of Minnesota. Guthrie decided to become a chemical engineer and worked hard to cover the costs of his studies. Under this program, he became for the first time interested in bacteriology and immunology. In addition, he started medical school. There, he met Dr. Henrici, the president of the American Society of Bacteriology, who opened him the position as graduate assistant at the University of Maine in Orono.

Guthrie was really happy about the "niche" which he had found and where he could work together with Dr. Stanislaus Sniezko, a microbiologist from the University in Krakow/Poland, who had received asylum in the United States. They recognized the importance of some bacterial species including widespread pathogens. Guthrie also worked to finalize his studies with a master's degree in biochemistry.

In 1942 Guthrie returned to the medical school at the University of Minnesota together with his wife Margaret; he had married her in Maine. In Minneapolis he completed his Ph.D. in bacteriology and his studies as medical doctor with the M.D. degree. Finally, in 1947 he got his first professional position as a research microbiologist at the National Institutes of Health in Bethesda/Maryland and could regularly earn a salary. But the main interest of Guthrie became biochemical genetic research.

After some academic positions at the University of Kansas, at the Staten Island Public Health Hospital, and at the Sloan Kettering Cancer Research Institute, he was finally in 1954 offered a much better position at Roswell Park Memorial Institute in Buffalo. Guthrie had a laboratory of his own and assistants to help with the work. He could continue with research on cancer and developed a screening method for compounds which could be used for the treatment in acute childhood leukemia. In 1958, 4 years later, Guthrie found the "niche", where he could remain for the rest of his professional life: The University of Buffalo Medical School and its Children's Hospital.

However, the Guthrie's second son John was a cause of continuing concern for the whole family.

Concern about John

Guthrie might never have become interested in mental retardation or mental disabilities without John. He was born in 1947 after a difficult pregnancy of Margaret Guthrie. It was immediately obvious that something was wrong with him. Like many other parents, Guthrie and his wife began to search for help in hospitals in the United States, but without success. Despite all efforts over many years, a conclusive diagnosis has never been confirmed.

John could successful attend special classes and later on do some work. He has undoubtedly influenced the career of some members of his family, getting very active in mental handicaps. John also added another dimension to the lives of the family, because they learnt patience and gained a deeper understanding of mental disabilities. His parents became quite active in the New York State Association for Retarded Children, where Guthrie met Dr. Warner, director of the Children's Hospital Rehabilitation Centre in Buffalo. He kept in touch with him, and Dr. Warner introduced Guthrie to PKU. Now, the way to the "Guthrie-test" was open.

A newborn screening test

Dr. Warner was primarily interested in a simple test procedure to monitor blood phenylalanine levels in PKU's under a phenylalanine-restricted diet, since the tests available were labour-intensive and needed a lot of blood. Only 3 days later, Guthrie reported to Dr.Warner, that he could do the test only needing some drops of capillary blood from a finger prick. He used filter paper discs, the surface of an agar culture gel and a specific strain of bacteria, which would grow, if excess phenylalanine was present in blood. Dr. Warner used this test in his efforts to treat more and more children with the PKU-diet. However, most of them were mentally disabled, because the diagnosis had come much too late.

In 1958 a coincidence occurred: the sister of Margaret Guthrie had a little girl, who was growing up quite normally in the first few months of life and showed then a delay in development. Finally, after about one year, the diaper test was done. Ironically, Guthrie's nice had PKU. This little girl played an important part in hastening him to develop a test procedure for newborn screening.

At this point, he started to simplify his bacterial test which was used to monitor the blood phenylalanine level under diet. Guthrie was convinced that the test should be as easy as possible to screen the blood samples from newborns before they left the hospital. He started with some tests at an institution for people with mental disabilities. Parents with PKU children and some doctors ultimately helped him to award grants which permitted Guthrie to organize a trial of the test procedure for 400 000 infants. Within 2 years, 29 regions of the United States participated and 39 cases of PKU were detected - an incidence of one in about 10 000 newborns, confirming Guthrie's estimate.

But soon, the first difficulties were arising. It was claimed that the test was not accurate and that some medical organizations did not want to dictate how a doctor has to practice medicine. Finally, in 1963 and after endless delays, a professional journal agreed to publish the method. Even after official recommendations to press for mandatory laws for newborn screening the opposition continued. Guthrie, however, was busy to develop tests for other disorders to prevent mental retardation.

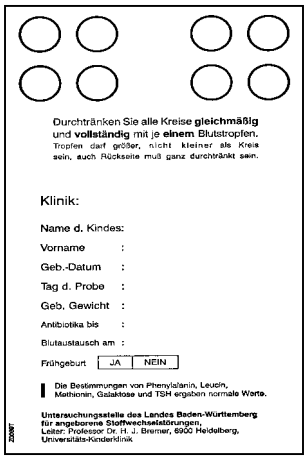
The closest assistant for many years was Mrs. Ada Susi. She had been a nurse in her native country Estonia and was since 1956 the head technician in Guthrie's laboratory. Mrs. Susi contributed considerably to the practical work to develop the test method.

But instead of being honoured for his tremendous work, Guthrie had to face new difficulties with regard to an agreement on the marketing and implementation of the PKU test. He became involved in lawyers, patent attorneys and politicians. Guthrie has never receipt a recompense for the whole work done to develop his bacterial inhibition assay for phenylalanine in a blood spot, since it was his goal to market the test as cheaply as possible. On the contrary: he bought for his laboratory one of the first punch-index machines to replace the manual work in the "Guthrie-test" procedure by an automation. This was a further revolution in neonatal mass screening.

Epilogue - "A crusade against mental retardation"

Guthrie started with his "crusade against mental retardation" already in 1960 at the occasion of an international congress in London - 3 years before the official publication of the test procedure in a pediatric journal.

At a later time the travelling costs of his trips were covered by grants, which enabled him to introduce the "Guthrie-test" for neonatal mass screening on PKU in many countries of the world. He could not only visit European countries, but also Latin America, China, Taiwan, and several times Japan, and even Australia and New Zealand.


Durchtränken Sie alle Kreise **gleichmäßig** und **vollständig** mit je **einem** Blutstropfen. Tropfen darf größer, nicht kleiner als Kreis sein, auch Rückseite muß ganz durchtränkt sein.

Klinik:

Name d. Kindes:
Vorname :
Geb.-Datum :
Tag d. Probe :
Geb. Gewicht :
Antibiotika bis :
Blutaustausch am :
Frühgeburt JA NEIN

Die Bestimmungen von Phenylalanin, Leucin, Methionin, Galaktose und TSH ergaben normale Werte.

Untersuchungsstelle des Landes Baden-Württemberg für angeborene Stoffwechselstörungen,
Leiter: Professor Dr. H. J. Bremer, 6900 Heidelberg, Universitäts-Kinderklinik

Fig.3:
The famous "Guthrie-card", developed by Robert Guthrie and published in 1963 as bacterial inhibition assay to detect phenylalanine in a blood spot. This was the first method to diagnose PKU on a population basis and made neonatal mass screening on PKU possible.

The list of his friends all over the world reads like a book on "Who is Who" - reflecting the early pioneers in this new field of pediatrics: Bickel / Germany; Cabalska (Barbara) / Poland; Cahalane / Ireland; Hudson / United Kingdom; Naruse and Kitagawa / Japan; Schmidt (Benjamin) / Brazil; Scott / United Kingdom; Smith (Isabel) / United Kingdom; Thalhammer / Austria; Tsagaraki (Sophia) / Greece; Veale / New Zeanland; Velazquez / Mexiko - just to remind of a few names of doctors with a strong commitment to establish newborn screening with the Guthrie-test in their countries.

It took some time until Guthrie found recognition. At last, schools and laboratories were dedicated to him and he received a large number of awards.

On June 24, 1995 the pediatric community lost an "Evangelist", who has saved by early detection thousands of children from mental retardation.

References

Guthrie R, Susi A. A simple phenylalanine method for detecting phenylketonuria in large populations of newborn infants. 1963. Pediatrics 32: 338 - 343.

Holt Koch J. Robert Guthrie - The PKU Story: Crusade against mental retardation. 1997. Pasadena CA; Hope Publishing House.

PKU
A summary of the present knowledge

- Phenylketonuria (=PKU) is the most common inborn error of amino acid metabolism in European populations, concerning the essential amino acid phenylalanine, which is a constituent of all natural proteins.
- Normally, phenylalanine is converted to tyrosine. This hydroxylation mainly takes place in the liver and is catalyzed by the enzyme phenylalanine hydroxylase.
- PKU is caused by an autosomal recessive deficiency of this enzyme, leading to an increase of phenylalanine in body fluids.
- Nowadays, more than 400 different disease-causing mutations in the phenylalanine hydroxylase gene have been identified; 29 of them are regarded as prevalent in the European populations.
- The mutations vary in their impact on enzyme activity.
- Therefore, a broad range of clinical phenotypes is observed, ranging from severe forms of PKU to so-called "mild hyperphenylalaninemias".
- The clinical features of untreated PKU are mental manifestations, for example retarded intellectual development, neurological abnormalities, and extraneural symptoms.
- PKU is detected shortly after birth by neonatal mass screening due to the elevated phenylalanine level in blood and concerns in the most parts of Europe at least 1 in about 10 000 newborns.
- The treatment is based on a phenylalanine-restricted diet - so-called "PKU diet" - which should be started immediately after confirmation of the diagnosis. This diet needs a very special range of products, consisting of phenylalanine-free amino acid mixtures to replace most of the natural protein intake, low protein dietary food, and some vegetables and fruits.
- It is obvious that the products involved in the diet are essential for all persons depending on this treatment. They and their families need a lifelong care in specialized units with an experienced staff to prevent mental retardation and other manifestations of this disorder.
- The enzyme phenylalanine hydroxylase needs for its normal functions tetrahydrobiopterin (=BH4) as cofaktor. Biosynthesis and regeneration of BH4 are well established.
- However, also for tetrahydrobiopterin "inborn errors of metabolism" are known, which occur very rarely. The patients develop a severe progressive neurological illness unresponsive to the phenylalanine-restricted diet. They have to be treated with the cofaktor tetrahydrobiopterin.
- Independent of the biosynthesis and regeneration disorders of BH4, it could in the last years be observed that a specific "tetrahydrobiopterin-responsive phenylalanine hydroxylase deficiency" is existing and that a so far unknown number of mutations is responsive to a treatment with BH4. The biochemical and clinical research in this field is going on and no final conclusions can yet be drawn.

<u>It should however always be kept in mind, that PKU is one of the very few disorders for which a treatment on a sound scientific basis is known and confirmed by innumerable investigations in the last 50 years. The diet is safe and effective and can prevent mental retardation. All persons afflicted have a right to help and support.</u>

The European Society for Phenylketonuria and Allied Disorders Treated als Phenylketonuria is a non-profit organisation with members in the following countries:

Austria	**Iceland**	**Slovakia**
Belgium	**Ireland**	**Slovenia**
Croatia	**Italy**	**Spain**
Czech Republic	**Moldova***	**Sweden**
Denmark	**Norway**	**Switzerland**
France	**Poland**	**The Netherlands**
Germany	**Portugal**	**Turkey**
Hungary	**Romania**	**United Kingdom**

* Applied for Membership in 2004

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