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The Discovery of Phenylketonuria: The Story of a Young Couple, Two Retarded Children, and a Scientist

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ABSTRACT. In the 1920s, a little girl 3 years of age was brought from China to the United States by her American mother. Although the child was beautiful, her mind was not developing. The grief-stricken mother had consulted doctors in China, but they could neither diagnose the problem nor provide treatment. Morning and night the same questions occupied her mind: “What is the matter with my little girl? What is causing it? Is there any doctor, anywhere, who can cure her?”

In the United States, she also went from doctors to psychologists to clinics looking for someone who could help. Finally, she went to the Mayo Clinic in Rochester, Minnesota. When she had answered all of the doctor’s questions, and all the tests were finished, they still could not tell her what was wrong. There was nothing they could do. The disease from which the little girl suffered was unknown at that time.

The mother was Pearl Buck. In her book, The Child Who Never Grew, 1 she described her first infant: “I remember when she was only 3 months old she lay in her basket on the sun deck of a ship. I had taken her there for the morning air. The people who promenaded on deck often stopped to look at her, and my pride grew as they spoke of her unusual beauty and of the intelligent look of her deep, blue eyes. I do not know at what moment the growth of her intelligence stopped, nor to this day why it did.”

This is a classical description of the disease, phenylketonuria (PKU). A perfect infant seems to develop normally for several months, then the development slows and at some point seems to stop. “Look at Mommy—look at Daddy!” the parents say as they try to coax the treasured smiles. Instead, the child drifts into a dream world and into irreversible mental retardation.

All Pearl Buck’s devotion and determination was of no avail in finding the cause of her child’s retardation. It was to be another mother with the same commitment to her beautiful but retarded children, who approximately 10 years later followed the same path until she found a special doctor who unlocked the secret of the fate of these children.

When 1 of the authors (W.R.C.) visited Miss Buck at her Pennsylvania home in 1960, she talked about how her daughter, Carol, then a grown person, had recently been diagnosed as having PKU, as a result of screening tests at the New Jersey Vineland Training School for the Mentally Retarded. During my visit and without disclosing the reason, Pearl Buck was invited to sniff a vial of phenylacetate crystals (the odor of stale urine samples from PKU patients). Immediately she recalled that Carol, as a child, had the same unusual odor. She was relieved that the prophesy of the last words in her book had come true: “What has been, need not forever continue to be so. It is too late for some of our children, but if their plight can make people realize how unnecessary much of the tragedy is, their lives, thwarted as they are, will not have been meaningless.”

These could be the words of Borgny Egeland, the mother of the children through whom the mystery of PKU was brought to light. Or they could express the conviction of the physician and biochemist, Asbjörn Folling, who believed that “what was not known could be known.” Through the discovery of PKU in these children, hope has been given to thousands of other children and to their grateful parents (Fig 1). Pediatrics 2000;105: 89–103; phenylketonuria.

ABBREVIATION. PKU, phenylketonuria.

It is now 65 years since the Norwegian doctor, Asbjörn Folling, discovered the cause of severe mental retardation in 2 young children, a sister and brother, in Oslo, Norway. The report he made in 1934 led to the identification of this disease in children all over the world—and to the subsequent development of a successful treatment. In Norway, the disease is called Folling’s Disease after its discoverer, and in the United States, it is called by the scientific name, phenylketonuria (PKU). How did Dr Folling discover the disease? It had undoubtedly been around for a long time and many doctors had seen such children. Behind the discovery are 2 human interest stories. The first is the story of Asbjörn Folling himself, a man humbly born but destined for greatness (Fig 2). The second is the story of a young
mother, Borgny Egeland, her husband, Harry, and their 2 retarded children (Fig 3A–D).

What was it that focused the attention and energies of us, the authors, on mental retardation, birth defects, genetic disorders, and now PKU? We confess that events in our private and professional lives influenced this. Not the least was the early loss of our second child with multiple birth defects and severe mental retardation. After this loss, we had started to write and teach about such problems and to develop a series of booklets for parents of handicapped children. Important, also, had been the influence of Dr Grover Powers, our beloved professor of pediatrics and mentor in the Yale University School of Medicine. Then, in the mid-1950s, we heard the wonderful news that a recently developed low-phenylalanine diet formula was preventing the mental retardation of PKU. The diet had been started in early infancy on an infant sibling of a retarded older child with PKU. This prompted us to devise and use a simple diaper test, whereby infants, in general, could be checked between 1 and 2 months of age. With this background involvement with PKU, it was natural, when the opportunity arose, to seek out Dr Fölling, to sit at his feet, to listen, and to learn.

This saga, as presented, is very much the result of deliberate personal encounters with the key participants. In the gathering of the following historical and biographical materials, we could not have been treated with greater, more openhearted cooperation (see “Acknowledgments”). Deep indeed is the appreciation of the authors!

THE STORIES BEHIND THE STORY

In 1958, after a meeting of the World Health Organization in Copenhagen, Denmark, I (W.R.C.) decided to take a ferry over to Norway on the chance that I would meet my hero, Dr Asbjørn Fölling. Preventing mental retardation was, to me, one of the greatest challenges of medicine. At that time, I was very involved in the early detection and treatment of infants with PKU. I wanted to know more about Dr Fölling and how he discovered this disease.

When I arrived in Oslo, Norway and made a call to the University Medical Center, I was told that Dr Fölling was on holiday at the shore. After I explained that I was visiting from the United States, I was encouraged to give Dr Fölling a call. This I did, and with evidence of friendly warmth behind his formal hospitality, he immediately invited me to come and join him at his cottage, where he and his family were celebrating his 70th birthday. I was 34 at the time.

It was a beautiful, warm, sunny day as I climbed aboard the coast route bus to enjoy a 2-hour drive through Norwegian towns and countryside on my way to the little island of Borøy, southwest from Oslo, and a stone’s throw from the coast. I got off on the mainland and found a taxi to take me a few miles, across a little bridge to the rocky island dotted with cottages. It all looked so much like the coast of Maine. With Dr Fölling were his wife, Guri, his daughter, Ragna, who had recently graduated from medical school, and his son, Ivar, a medical student. Other more distant relatives and long-time friends also were present. The special gathering, however, was beginning to break up and disperse.
Dr Fölling and I spent several hours talking about the discovery of PKU, the chemistry of the disease and the later efforts to treat it. He was interested in the children I was treating at the time. I shared with Dr Fölling the exciting encouragement we had been experiencing with our diaper test screening in the California Health Department Well-Baby Clinics—and of the good results with low-phenylalanine diet formulas. (My research diet powder was Clinical Product CP 3097-A, later marketed by Mead Johnson and Company as Lofenalac.) Dr Fölling was very interested and was obviously keeping informed on early detection efforts and the developments in diet management.

When Mrs Fölling called us to lunch, we talked together about life in Norway and the United States in easy good spirits as we enjoyed the garden and the view of the cove, which was next to the house. Dr Fölling always spoke thoughtfully in a quiet, reserved manner. Guri Fölling, approximately 15 years younger than her husband, was the picture of a charming hostess and helpmate. I felt very privileged to have shared this holiday retreat with this very special Norwegian family. I treasure the picture that I took of them that day (Fig 4).

Having thought that I would probably never see Asbjørn Fölling again, I went back to California to continue working on an infant-screening program for PKU, which used the ferric chloride test on freshly wet diapers. In the process, many pediatricians and public health physicians were being educated about PKU, and through these early efforts additional infants with PKU were diagnosed in California and successfully treated.

A year later, in August 1959, the American Association on Mental Deficiency sponsored the First International Medical Conference on Mental Retardation. This was held in Portland, Maine. My wife, Dr Siegried Centerwall, and I were going, as were many others interested in mental retardation. It occurred to me that Dr Fölling should be at that meeting. Because I was trying out the experimental low-phenylalanine diet (Mead Johnson and Co) with the infants I was treating, I knew that Mead Johnson and Co had special interest in PKU. I asked Dr Frank Lyman, their medical consultant, if he thought the company...
would be interested in sponsoring Dr Fölling, so that he could attend the meeting. The company readily agreed and invited Dr and Mrs Fölling to come to the United States at the expense of Mead Johnson and Co. Consequently, the conference invited Dr Fölling to be a moderator and speaker at the meeting (Fig 5).

It also turned out to be a time when we could return the hospitality of the Föllings hospitality because Brunswick, Maine (20 miles from Portland) was where the author, Siegried Centerwall, grew up and where her mother still lived. We invited Dr and Mrs Fölling to stay with us there and also arranged to have them stay a couple of nights at the Harriet Beecher Stowe House, which had long been converted into a travel lodge and gift shop and was located directly across the street from our family home. Mrs Stowe had written *Uncle Tom’s Cabin* while living there during the middle years of her life.

One evening, we invited some friends and colleagues who were attending the conference and who had a special interest in PKU to come and spend some time with Dr Fölling. After dinner, we asked him to tell us all exactly how he happened to discover PKU.

Dr Fölling sat in the middle of the sofa, while around him gathered Dr George Jervis, who was 1 of the first to study PKU in the United States and had identified the liver enzyme defect of PKU, which obstructed the normal conversion of phenylalanine to tyrosine;2 Dr Clemens Benda, a recognized specialist in mental retardation; Dr Gunnar Dybwad, the Executive Director of the American Association on Mental Deficiency; Dr Frank Lyman, pediatrician medical consultant to the low-phenylalanine diet project of Mead Johnson and Co; and Dr Horst Bickel, a German National residing in England, who, in consultation with British scientist, Dr L. I. Woolf, was the first person to make a low-phenylalanine food and treat a child with PKU. Some wives were also present. Dr Fölling expressed surprise that we really wanted him to tell his story, which, after urging, he did in his precise, unassuming manner. Some of the details in the present memoir were told that evening. Meanwhile, a more abbreviated report about the discovery of PKU was being first published in our article in 1961.3 After he finished his story, he was asked if the rumor that he was related to the Egeland family was true. He informed us that when he started to study the children he was not aware of
any connection, but then he found out that his nephew’s wife’s brother was married to Mrs Egeland’s sister (Fig 6).

I sensed that I wasn’t the only one who had fallen under the spell of this man who had opened up the way for the rest of us. His great charm was in his simplicity of manner, despite the great depth of his learning and thought. His conversation showed that he had many interests and had done a lot of reading in a variety of fields. Even so, he seemed to be a very humble person. Also, he liked to support his philosophical bent with quotations that expressed his interest in human nature. He changed the old saying “knowledge is power” to “knowledge is humility.”

Dr Fölling already had received many honors in his lifetime. He was made an honorary member of the Norwegian Medical Society. In 1950, King Haakon VII of Norway and the National Scientific Society presented Asbjörn Fölling the first Friotjot Nansen medal, named for the famous Norwegian explorer and scientist who studied the arctic oceans. Fölling was an explorer of the inner ocean of the human body, and he was honored for his studies in human metabolism.

ASBJÖRN FÖLLING

The Making of a Physician-Scientist and Viking-Explorer

Reflecting on the life of a man such as Dr Fölling also gives an opportunity to appreciate the generation before ours when important strides in medical science were made by individuals with relatively little basic scientific information, very little equipment, and almost no technology. They worked in the laboratory as their clinical colleagues worked at the bedside, with few tools, but with a firm grasp of principles and disciplined observation and reasoning. To better understand Dr Asbjörn Fölling, the research-minded mature man, let us look back on his youth and family life, his boyhood responsibilities, his schooling, his values, and the hurdles along the way.

Childhood on the Farm

The hero of this Norwegian saga was born August 23, 1888, youngest child on a family farm in the middle of Norway. He had 1 older brother, and 3 older sisters. He was named Ivar Asbjörn Fölling—Ivar after his father and great grandfather, Asbjörn, the name by which he was known. Fölling was used as the last (family) name from the name of the farm, it being the custom in those days to take the name of the place where one lived.

The Fölling farm had a large double homestead and a separate cow barn across the farmyard. There were other farms on the sides of hills that went upward to the east from the ocean inlet in the valley below. Nearby was the white wooden church with a tall graceful spire, surrounded by gravestones of generations of Föllings and those of other farm families nearby.

Asbjörn remembered how their farm had many uncles and aunts living there. The growing children all helped run the farm. This way the work did not seem very hard. People were used to living simply and sharing what they had. The grandparents and sometimes an older unmarried uncle lived in the smaller side of the house. All the women helped with cooking, preserving, cleaning, sewing, and knitting.

It was great fun for a little boy like Asbjörn to run around with his brother, sisters, and cousins. In summer, they played in the fields, and in winter, they slid down the snow-covered hills bundled up in colorful hand-knit sweaters, caps, and socks. But soon Asbjörn had to work like the rest of the children. One day he was carrying in the wood when his mother said to him, “Today you are 5 years old.” It was his birthday and that was all that was made of it. When he was older, he worked as a cowherd, taking the cows out to the pasture up in the hills. After the early morning milking, he would drive them out and watch them all day, while his sisters would make the rich milk into cheese to keep for the winter. In the evening, Asbjörn would drive the cows home and help with the milking. It was a long day.

Christmas was the great festival of the year and a very exciting time for the children. There were special church services and music. His mother, aunts, and sisters made many good things especially for Christmas: lutefisk (a bleached white fish preserved with lye), fattigmand (fried pastry), and spritz cookies made into an “A” for Asbjörn. At Christmas, there were new clothes, and the children would eat with the adults and go with the family in the evening to visit friends. One year after the special mulle berries with whipped cream was served for dessert, poor little Asbjörn was crying. Why? Because he already had eaten too much and he didn’t have room for any more. I (W.R.C.) confess that as a boy raised by my Norwegian family in America, I really enjoyed fattigmand but sure didn’t like lutefiske!

The Student

As Asbjörn grew, he had more time for his studies than his older brother and sisters who were needed to do the work at home. He went to school approximately 2 miles away, below the church hill toward the town and ocean inlet—walking with children from other farms near his home. He went to the 1-room school every other day. This made it possible

Fig 6. The relationship between Dr Fölling and the children first discovered to have PKU—a chance relationship through marriage and not genetically related.
for all the youngsters in the area of all ages to attend. Even for Norwegian children, it was a long, hard trudge in the cold and snow. Often they went on their skis or on snowshoes.

Asbjørn liked school and did well in the country school, which went through the ninth grade. When the older children had finished the upper class at the local school, they had stayed home to help on the farm. But being the youngest son, Asbjørn, was allowed to go on with his studies in Trondheim, where he stayed with his oldest sister. She had gone there to live after she got married. Trondheim, the ancient capital of Norway, was approximately 50 miles from the Følling farm. There he finished the tenth, eleventh, and twelfth grades.

He was never a very strong boy, and about the time he finished high school, he was discovered to have tuberculosis. The doctor said he must rest for a year. At that time, there was no other treatment. There was to be no farm work or studies. It might be much longer than a year, and he might not even survive. But for Asbjørn it was a time when he could think about what he wanted to do. He did survive, and he decided that he didn’t want to be a farmer. He wanted to go on with his education and be a scientist, but he was afraid that his parents, sisters, and brother wouldn’t agree. They might think that he had been pampered a bit too much already and should now take his place helping on the farm, where he was needed more because the old people could no longer pitch hay or bring in the cows and milk them.

He heard about the new Technical College of Norway that was soon to open in Trondheim and he wanted to go there. When the doctor said that he was well, he talked to his father. His father shook his head and told him the obvious—that he didn’t have the money to support a son in college. But Asbjørn was so determined that he asked if he could try to work his way through by tutoring younger students. He would come home in the summer and work on the farm. And so it was decided, and the farm boy left to join the new institute in the beautiful old city of Trondheim, where the medieval cathedral was already 900 years old. The college still stands high on a hill and takes students from all over Norway. They live, study, and work in many new buildings but also in the large gothic stone structure, which was the original college.

There were only a few students in his class, which was the first to be enrolled. Asbjørn majored in chemical engineering and was proud to be a member of the first graduating class. His family was proud too, and now they looked forward to his settling down, if not on the farm, then in Trondheim. But Asbjørn did not have settling down in mind. He wanted to further his education in Oslo at the University. It would be expensive to go to the capital. He asked his father for a small loan, which he received, but he did not tell him that he had decided to study medicine. His father thought he needed the money to get started in the big city.

The next year, when he again approached his father for some money, his brother challenged him to tell what he was doing. He then confessed that he was teaching chemistry at the Dental College and studying medicine at the Medical College of the University of Oslo. Fortunately, the father admired his student son, and he wished him well. In his heart, Asbjørn was always close to his family, and he loved to go back to the farm.

The Researcher

Even after he received his medical degree, Asbjørn continued to teach and to conduct research at the Dental College. His family believed that he was inhibited by his country background and that he could not compete with the city-bred professors. Nothing could have been further from the truth. With his special training in chemistry, which was the key to modern medicine, he was a competent researcher and respected for his work. He was asked on several occasions to join the medical faculty, which he did later in life. Meanwhile, however, he had stayed in close contact with work being performed by his colleagues in medicine.

Asbjørn Følling was one of the first physicians in Norway to apply chemistry to the study of medicine. He came to the United States in 1928 on a Rockefeller Foundation Fellowship and studied under American medical researchers at Harvard, Yale, Johns Hopkins, and the Mayo Clinic. He went home to Norway the next year but returned to the United States in 1930 to work with Dr Lawrence Henderson. Dr Henderson, a Harvard biochemist and physiologist, best remembered for the Henderson–Hasselbalch Equation, was doing research in high-altitude physiology in Colorado. They also were studying marathon runners (Fig 7).

Guri Opsahl entered Asbjørn’s life when she was a young nurse in training at the University Hospital in Oslo and was sent to get some special medication from the researcher, Dr Følling. She was impressed with his dignity and kindliness but was quite in awe of him and did not dream that they would become friends. He was evidently impressed with her too, although they really did not become personally acquainted for several years. He may have thought that she was too young and that his future was not yet settled. In fact, it was not until 1931 after his second trip to the United States that they married. Shortly after their marriage, Asbjørn was awarded another scholarship, this time to study in Vienna. His bride went with him.

By 1934, Dr Følling and his wife had bought a pleasant apartment in Oslo, where they lived together for 39 years. Guri was busy with their 2 children, as Asbjørn was establishing himself as a teacher and researcher in the chemistry of disease. In 1934, Dr Følling was contacted by Borgny Egeland about her 2 retarded children.

THE EGELEN FAMILY

Special People—Special Involvement

Two Retarded Children

Borgny and Harry Egeland were married in 1923 soon after Harry graduated from the dental college
in Oslo. He had been the youngest of his class. Borgny Egeland, like most young women in those days, was glad to give up her own work and devote herself to their home and raising a family. They were young and fun loving and very happy. Their happiness grew when a sweet little girl was born. They played with her and walked her in her carriage in the park without a thought that anything might be wrong with their little Liv.

When the little girl was nearly 3 years of age, they wondered why she had not begun to say words. When they told the doctor of their concern, he reassured them that she would talk later. Why, he himself didn't talk until he was 3 years of age! But Liv did not talk at 3 years old, or ever.

At about that time, Borgny had become pregnant again and their little boy Dag was born 3 years after his sister. He was normal and alert for a few months but then seemed to weaken and lose interest in his surroundings. He had become frailer than his sister had been at that age. Liv had walked at the 16 months of age, but little Dag never even sat up by himself. He was very difficult to feed and although he grew physically and was a handsome little boy, he remained mentally like an infant until death at 6 years of age.

It was when Dag was an infant that the parents became increasingly aware that both of the children had a strange musty odor to their urine and began to think that whatever was causing this odor might also be causing their children to be mentally retarded. Their sympathetic family doctor couldn't offer any explanation for the odor or the children's retardation.

The Search for Help

When it was apparent that little Dag was even more tragically affected, the mother began to look for another doctor and then yet another. But the story was the same as with the first doctor: They, too, didn't find any explanation for the condition of the 2 children. Dag was admitted to the University Hospital in Oslo for several days at 2 years of age and tests were performed. When all the doctors failed them, still the mother would not give up. In desperation, she called in a nonphysician healer and then another. One was a woman, well known in Oslo, who came twice and gave the children herb baths and herb teas. The other was a man with a reputation as a visionary. He came once, but to no avail. Borgny Egeland was in despair. What could they do now? Where could they turn?

In the dental college, Harry Egeland had taken a course from Professor Asbjørn Følling and was aware that he was doing research in metabolic diseases. He and Borgny talked about the possibility of having Dr Følling see their children. Borgny knew that her sister saw Dr Følling occasionally at the house of a relative. (What Borgny didn't know at the time was that this relative had distant marriage ties to Dr Følling's nephew.) Borgny asked her sister if she would speak to Dr Følling, when she had an opportunity, and explain about the children and their odor and ask him if he thought there was a link between the odor and the retardation of the children. This she did. Dr Følling replied that he had never heard of such a disease, but he politely offered to examine the urine if Mrs Egeland would bring a sample to his laboratory at the University Hospital.

THE DISCOVERY OF PKU

When a sample of the urine from the older child was brought to his laboratory by Borgny Egeland, Asbjørn Følling did not know that he would have the chance to discover an unknown disease. He probably thought that he would discover nothing at all. The routine urine tests for albumin, blood, pus, acidity, and sugar were normal. Then to a small, acidified urine sample he added a few drops of aqueous ferric chloride solution (a salt of iron) that is used as a test
for ketones in the urine, which are abnormal substances that make a red–brown color with ferric chloride. Instead, the little girl’s urine turned a dark green color that faded in a few minutes. This physician–chemist had never seen such a reaction before. Obviously something unusual was in this urine.

Did the little brother, Dag, have the same thing in his urine? Dr Folling asked the mother to bring in a sample of Dag’s urine. The excited mother came right away. The little boy’s urine gave the same unusual color with the solution of ferric chloride. He looked in his chemistry books but such a reaction was not described.

He wondered whether the green color could be attributable to any medicines that the children had taken. Aspirin in the urine can give a color, usually purple, with ferric chloride. The mother gave the children aspirin occasionally, and some herbs and tonics that had been recommended. “Take them off all these things. Do not give any medicines for the next week and then bring some new urine,” he requested. The second samples gave the same color when tested. There was an unknown substance in the urine and the next step was to try to find out what it was (Fig 8).

Dr Folling then asked Mrs. Egeland to bring in a urine sample every other day, which she did for approximately 2 months. “She brought me about 20 liters of urine in all,” Dr Folling recalled. “Day after day I worked to isolate the unknown substance.” But isolating it wasn’t easy. He soon found that when he tried to evaporate his solution to crystallize the substance, it oxidized rapidly to a brown spot in the test tube. In 1 of his articles he described the process he used:

The urine was saturated with sodium chloride, acidified with hydrogen chloride and extracted with ether. Next, he extracted with sodium carbonate, acidified again, and extracted with ether. Some impurities were removed with hydrogen chloride and water, and the ether was dried and evaporated. Now the substance could be recrystallized from a chloroform/benzene mixture. All these operations were done keeping the products in a nitrogen atmosphere; otherwise the substance would have been destroyed by oxygen from the air. During the extractions, the ferric chloride reaction indicated the continued presence of the substance. After six recrystallizations, the melting point became constant, at 155°C (311° F), suggesting that a pure substance had been obtained.

He then proceeded with the chemical analysis, which showed that there was just carbon, hydrogen, and oxygen in the relationship: 9(C)-8(H)-3(O). This also conformed to the molecular weight obtained by titration with a base, assuming a molecule with a single acid radical. Earlier, he had noted when the impure unidentified substance stood for a few days in the air, the odor of benzaldehyde (COOH) came off. He reasoned this was a product of mild oxidation. And when gently heated with potassium permanganate in alkaline solution, oxalic acid (COOH) and the characteristic crystalline appearance of benzoic acid (COOH) were obtained as products of stronger oxidation. From reactions that give benzaldehyde and benzoic acid, he came to the conclusion that the substance had a benzene ring and was probably phenylpyruvic acid. When some known phenylpyruvic acid was added to the unknown substance, the melting point and properties were not altered, proving that they were the same. (Of note, phenylactic acid or phenylacetate, a by-product of urinary phenylpyruvic acid, is the substance responsible for the musty odor of PKU. The odor is not typically present in freshly voided urine.)

Asbjorn Folling had not forgotten that the reason for finding the substance in the urine was to discover whether there was a connection between the substance and the mental retardation of the Egeland children. Therefore, he contacted institutions in and around Oslo that cared for mentally retarded persons. Among 430 children tested, he found 8 with the same abnormality as the Egeland children, including 2 more sibling pairs. In 1934, he published papers in both the Norwegian and German scientific literature that set forth these findings—approximately 6 months after the time that Borgny Egeland had first contacted him.5 Liv, the girl, was then 7 years old and her brother, Dag, was 4 years old. Dr Folling called the condition “imbecillitas phenylpyruvica” because of the serious mental retardation and phenylpyruvic acid in the urine (Fig 9A and B). Within several years the name “phenylketonuria” was coined by Dr Lionel Penrose, eminent geneticist of England, because of the characteristic appearance of

Fig 8. When a few drops of 10% aqueous ferric chloride solution was added to a small acidified sample of the children’s urine in a test tube, an immediate dark green color appeared that faded within a few minutes. This did not occur in the urine samples from normal persons.
the phenylketone, phenylpyruvic acid, in the urine. The later use of the abbreviation PKU has been credited to the US lay-writer team of Becker & Becker in magazine articles of the late 1950s.

Dr Fölling's landmark discovery identified an error in human protein chemistry and showed that this metabolic error could cause mental retardation. Because PKU is often found in more than 1 child in a family, he was able to show, by analyses of multiple pedigrees, that it occurs by simple autosomal recessive gene inheritance. Mentally retarded children in institutions all over the world were checked with the ferric chloride test of the urine and in most western countries a positive test result was found in 1% to 2% of seriously retarded persons.

EARLY DETECTION AND SUCCESSFUL TREATMENT OF PKU

For many years, PKU was considered an unfortunate disease of mental retardation for which nothing could be done. But by the mid 1950s, a special diet food had been developed and soon infants were successfully treated to prevent the mental retardation of PKU. To be successful the diet had to be started in early infancy before the onset of mental retardation.

The infants were mostly the young brothers and sisters in families with an older retarded child with PKU. The motivation of these parents in following the diet was very high and the gratitude of the parents made this work a very special joy for the doctors, nutritionists, and other team members. A drawing of the phenylalanine metabolic pathway helps to explain the laboratory and clinical findings in PKU and the need for very early case detection followed by prompt dietary treatment (Fig 10).

PKU is called an “error of metabolism” because children who have it cannot use (metabolize or break down) phenylalanine, an amino acid making up approximately 5% of all protein foods. PKU is also called phe (pronounced fee) for short. The inability to use or break down phe, if untreated, causes a much increased phe level in the blood, called hyperphenylalaninemia or hyperphe (meaning high phe). Hyperphe is responsible in some way for the mental retardation, which PKU causes. Children with PKU are normal at birth, but if the infant is not treated, he or she does not develop mentally as expected. The child looks normal physically but is slow to sit and crawl. Some slowness in developmental abilities may

![Fig 9. A and B, The first children (Liv, 7 years of age, and Dag, 4 years of age) to be diagnosed with PKU—from the 1954 publication of Dr Fölling on the discovery of PKU.](image)

![Fig 10. Metabolic pathway of phenylalanine in the body. The high phenylalanine blood levels cause abnormalities such as brain dysfunction (mental retardation, irritable and destructive behavior, and occasional convulsions), pigment metabolism (lighter coloring of skin, hair, and eyes), and unusual substance in the urine giving diagnostic test results.](image)
be apparent by 4 to 6 months of age; and by 2 to 3 years of age, most of these children are moderately to severely retarded.

PKU is caused by abnormal genes inherited from the parents. These PKU genes cause a substance in the body, called an enzyme, to be missing or abnormal. The enzyme, phe-hydroxylase, is necessary for the normal use of phe—it changes phe to other substances used by the body. Everyone absorbs phe into the body from food. In normal people, the amount of phe in the blood is always low (usually between 1 and 2 mg%). As soon as infants with PKU began to take milk (breast milk or cow milk), the phe begins to build up in the bloodstream like water behind a dam. Within weeks, it reaches a very high level, 20 to 30 times higher than normal. Then, like water over a dam, some of it spills into the urine as phenylpyruvic acid and other chemicals.

How were newborn infants with PKU to be found when there was no older brother or sister with PKU? Screening young infants with the ferric chloride test fairly recently wet diapers began in California in the late 1950s. This diaper test, with a drop of ferric chloride solution (or the use of Phenistix dipsticks developed by Ames Company and pressed against the wet diaper), could not consistently be accomplished until the infant was a few weeks old because the phenylpyruvic acid usually didn't appear in the urine until then (Fig 11A and B). Thus, many infants did not get tested. What was needed was a blood test that could be performed while the infant was in the hospital newborn nursery. Such tests were developed in the early 1960s (Fig 12A–D). In the following years, 1 state after another passed laws requiring infants to be tested for PKU before they were discharged from the hospital. Today all 50 of the United States, the District of Columbia, and Puerto Rico have newborn-screening programs for PKU, and in all except the states of Maryland and Wyoming, the tests are mandated mostly by law (with a few mandatory by regulation). Every year in the United States, approximately 300 newborn infants with PKU are diagnosed and mental retardation is prevented by diet treatment started soon after birth.

Up to the present time, approximately 40 of the 50 states have been using the Guthrie bacterial inhibition assay test with the remainder using the McCaman–Robins fluorimetric test method. And with PKU as an example and model, newborn-screening tests have been devised and used for an additional half dozen or so serious metabolic disorders for which early treatment also can prevent mental retardation. In addition to PKU, these disorders are now being included in mass newborn-screening programs. The result, in the United States alone, is, the discovery and mind-saving treatment of more than 1000 infants each year. And in at least 20 other nations of the world, similar newborn screening and treatment programs have been and are being developed.

The construction of this path of progress and success over these many years has been accomplished only by the deep concern and concentrated efforts of scores of dedicated researchers and clinicians throughout the world. In this article, which focuses primarily on the initial discovery and identification of PKU, mention is made of only a few of the earliest pioneers in the history of PKU, the development of effective dietary prevention of mental retardation, the subsequent successful early mass screening and continued improvement for PKU and other disorders, the successful location of the phenylalanine hydroxylase gene on human chromosome No 12, and the ability for prenatal diagnosis and carrier detection of classical PKU. In the many decades that followed, these and scores of other researchers have each continued to produce scientific and clinical reports on PKU.

The exciting event within the present decade has been the development of the tandem mass spectrometry of plasma extracted from dried blood spots. This method of early detection of multiple metabolic disorders, including PKU, is proving to be technically and economically feasible and to be faster, more sensitive and with better accuracy than the bacterial inhibition assay of Guthrie. Laboratories using the new mass spectrometry are testing mostly for 16 different disorders as effectively as testing for 4 or 5
conditions has been with the older techniques. In fact, already some countries including the United States, England, Germany, and Australia are using this new method with anticipation that this will replace the bacterial inhibition assays and the fluorimetric techniques of Guthrie and McCaman–Robins, respectively, which have been so valuable during the past half century. This is despite expensive start-up costs of the new laboratory equipment (approximately 250 000 US dollars per lab set-up with a doubling of this to include back-up equipment as might be needed).

**EPilogue**

**The Egelands—A Tale of Tragedy and Triumph**

Although it was through the persistence of the Egeland parents and because of their affected children that PKU was discovered, the resultant mind-saving treatment came too late for them. The disabilities of his children had taken a heavy toll on Dr Harry Egeland. At that time, without state-paid health services, he worked long hours to earn money to pay for the children's medical care, as well as home-nursing help because his wife could not manage for the 2 children night and day by herself. But even more trying was the effect that the stress, worry, and sorrow had on his asthmatic condition, which worsened as the years went by.

Two years after the discovery of PKU, little Dag died of pneumonia but Liv continued to live at home with her parents. Unfortunately, after approximately 20 years of age, Liv became much more irritable with attacks of anger and destructiveness. They had to consider admitting her into an institution, something they both hated to do. As she got worse, her father's health became worse. At last, they placed Liv in a home near Oslo, but alas, only 2 weeks later Harry Egeland died. He was only 46.

Borgny visited almost every week, taking Liv her favorite smoked salmon and cake, and the recordings of music she loved. They also went on long walks. The death of her daughter at age 51 was a great sadness for this lovely and loving woman who had never remarried and had only the 2 children. She was 74 at the time. She lived on in Oslo for another 13 years, dying in 1991 at 87 years of age (Fig 13).

Her dedication to her own children and the benefit that this brought to others was commemorated in Norway in 1984 at the 50th anniversary celebration of the discovery of PKU. The joy and satisfaction of this remarkable woman was immense as she read, "If you, Mrs Egeland, had not had the concern and determination 50 years ago to find the reason (and hopefully the cure) for the retardation in your 2 children, Dr Folling would never have made this..."
important discovery! You did not take “we don’t know” for answers. You persisted in your quest; and as a result, today thousands of persons and their families are blessed by normal lives and happiness. The sorrow and frustration you experienced in the mental retardation of your 2 children should now be tempered by the realization that their lives were not wasted; they did not live in vain! In a true sense, they suffered so that many might benefit!”

During the remaining twilight years of her life, Borgny Egeland rightfully received attention and recognition for her important role in the discovery of PKU—in television interviews and in newspaper and magazine articles. She also received Norway’s Frambu Health Center’s honorary “Mother and Child Statue” recognition. And the Norwegian Academy of Pediatrics awarded her a special statue of a ferret, depicting the tenacity and determination of this wonderful lady and mother, who led to this great discovery (Fig 14).

Asbjørn Folling—A Man for the World

The man who made this possible, Asbjørn Folling, led a long and productive life. He had pursued his career and family life in humble dedication.

He knew the Bible well and was religious in his living as well as his beliefs. He liked to quote his mentor, renowned biochemist and physiologist, Dr Lawrence Henderson who said, “I’d rather believe and be wrong, then not believe and be wrong.” Dr Folling was concerned with what was meaningful and worthwhile in life. He said, “You shouldn’t put sticks in the wheel of the Lord,” meaning you shouldn’t interfere too much in the Lord’s work. He also didn’t like to see nature interfered with. “I wouldn’t misuse anything,” he said. “Give back to the earth.” And give back he did, to his family, to his work, and to the world.

For his medical research and for the discovery of PKU, Asbjørn Folling received many honors in Norway, Europe, and the United States. In 1962, at a special dinner in Washington, DC, President John F. Kennedy presented Dr Folling with a special award for the discovery of PKU (Fig 15). The award from the Joseph P. Kennedy Jr. Foundation was symbolized by a glass statue of the winged seraphim, Raphael, the angel of science, healing and love (Fig 16). The citation read, “Dr Ivar Asbjørn Folling, retired Chief of the University Hospital Clinical Laboratory at Oslo, Norway, for opening a new era in the study of mental retardation with his discovery of the disease phenylketonuria, or PKU. His findings indicated a metabolic error was responsible for some forms of mental deficiency. As a result of his work, many other biochemists, clinicians and geneticists have been led to concentrate on the investigation of metabolic errors.”

Dr Asbjørn Folling went back to Norway aware that his careful work as a scientist and his concern for 2 handicapped children had been recognized as important steps in modern medicine that had opened
the way for the successful prevention and treatment of diseases, which cause mental retardation in children.

On January 24, 1973, Dr Fölling died, with his children and grandchildren around him, in his home in Oslo. He was 84½ years old.

As he had requested, his remains were taken back to the farm in Fölling and interred in the nearby church yard. Later, in fulfillment of his wish, a simple fieldstone from the farm was placed above his grave with just his name, Asbjørn Fölling, and the dates of his birth and death: “Asbjørn Fölling 23-8-1888 24-1-1973” (Fig 17).
On the 50th anniversary year of his discovery, a memorial to the event was erected in Asbjørn’s hometown of Steinkjær, approximately 8½ miles (14 km) north of the Folling farm in central Norway. From left to right in this newspaper photograph are the commemorative speakers on this occasion: Dr. Ivar Folling (son of Asbjørn), Dr. Willard Centerwall (US professor and family friend), Sverre Lie (pediatric PKU specialist in Norway), Guri Folling (the widow of Asbjørn), and Erik Bartnes (the mayor of Steinkjær).

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Borgny Egeland: Widowed mother of Liv and Dag, the first children to be discovered to have PKU—several personal interviews and conversations with authors (S.A.C. and W.R.C.) during the 1980s and 1990s in Norway and the United States.

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