Robert Guthrie (1916–1995) [1]

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Robert Guthrie developed a method to test infants for phenylketonuria or PKU in the United States during the twentieth century. PKU is an inherited condition that causes an amino acid called phenylalanine to build to toxic levels in the blood. Untreated, PKU causes mental disabilities. Before Guthrie’s test, physicians rarely tested infants for PKU and struggled to diagnose it. Guthrie’s test enabled newborns to be quickly and cheaply screened at birth and then treated for PKU if necessary, preventing irreversible neurological damage. After developing the test, Guthrie traveled the world to advocate for mass screening for PKU in newborns. Along with his PKU test, Guthrie developed newborn screens for maple syrup urine disease and for galactosemia. Guthrie’s test for PKU and campaign for newborn screening led to the early diagnoses of PKU in thousands of infants, preventing those infants from developing mental disabilities.

Guthrie was born to Ina Florence Ledbetter Guthrie and Reginald Guthrie in Marionville, Missouri, on 28 June 1916. Due to his father’s traveling job as a salesman, Guthrie’s family moved from place to place throughout Guthrie’s childhood before settling down in Minneapolis, Minnesota, in 1922. According to his biographer Jean Koch, Guthrie learned the skills and techniques of a salesman from his father. In Minneapolis, Guthrie graduated at the bottom of his high school class in 1935.

After graduation, Guthrie returned to high school to finish the requirements for admission to the University of Minnesota [3] in Minneapolis, Minnesota. In the spring semester of 1936, Guthrie began studying at the University of Minnesota [3] under the National Youth Administration program, which provided low-income students with federally subsidized jobs at state universities. Guthrie studied astronomy and microbiology when he started college, and he planned to major in astronomy and minor in microbiology. However, after taking a job with Charles Evans in the department of bacteriology and immunology, Guthrie majored in microbiology.

Evans encouraged Guthrie to attend medical school after graduation, and in 1939 Guthrie enrolled in the medical school program at the University of Minnesota [3]. Guthrie disliked medical school and transferred to the University of Maine in Orono, Maine, less than a year later, to work towards a master’s degree in bacteriology. In 1941 during his time at the University of Maine Guthrie met Margaret Flagstad, who sat next to him in organic chemistry, and the couple married in August of 1941. The same year, the couple returned to Minneapolis, where Guthrie finished his medical degree at the University of Minnesota [3]. In 1945, Guthrie and his wife had their first son, Tom, in Minneapolis while Guthrie was in medical school. Guthrie spent an extra year at the University of Minneapolis to pursue a PhD in bacteriology before graduating in 1946 with a medical degree and a PhD. Between 1941 and 1946, Guthrie earned six degrees in six years: a bachelor’s degree in bacteriology, a bachelor’s of science, a bachelor of medicine degree, a master’s degree in biochemistry, an MD, and a PhD in bacteriology.

One year after graduating, in 1947, Guthrie began his professional research career at the National Institutes of Health [4] (NIH) in Bethesda, Maryland, studying the protozoan Trichomonas fetus [5], which causes spontaneous abortions in cattle. Guthrie’s supervisor had no interest in his research project on protozoan, and Guthrie eventually dumped his cultures of protozoan down the sink and quit his job at the National Institutes of Health [4]. In 1949, after his time at the National Institutes of Health [4], Guthrie took a position as chairman of the department of bacteriology at the University of Kansas in Lawrence, Kansas. Guthrie changed jobs several times between 1950 and 1954. During those four years, he moved from supervising the diagnostic bacteriology laboratory at the Staten Island Public Health Hospital in Staten Island, New York, to supervising the diagnostic bacteriology laboratory at the Sloan Kettering Institute in Manhattan, New York. He then moved to Roswell Park Cancer Institute in Buffalo, New York, to develop chemotherapeutic agents to treat cancer.

Between 1947 and 1954, Guthrie and his wife had five more children. Their second child, John Guthrie, was mentally disabled but hadn’t been diagnosed with a birth defect or disease, though he visited numerous physicians and underwent several tests. His son’s mental disability prompted Guthrie to work with the National Association for Retarded Children, headquartered in New York City, New York, a national organization [6] that advocated for and served people with intellectual and developmental disabilities and their families.

In 1954 Guthrie’s son, who was seven years old, attended a private school run by the Eric County chapter of the New York State Association for Retarded Children. Most public schools did not have programs for mentally disabled students. Guthrie participated in the local Williamsville Parent Teacher Association, where he collaborated with other parents to create a class for mentally disabled children in public schools. In 1957, the Academy School for children, a public school in Williamsville, New
York, organized a special class for children with mental disabilities.

In 1957, Guthrie and his wife took their mentally disabled son to a children’s rehabilitation center directed by Robert Warner, the director of the Children’s Rehabilitation Center at the University of Buffalo Children’s Hospital in Buffalo, New York. Although Warner did not diagnose Guthrie’s son, he talked with Guthrie about phenylketonuria, a congenital metabolic disease hypothesized to cause neurological damage. In 1934 Ivar Folling, a physician in Norway, had described PKU. PKU People with PKU lack phenylalanine hydroxylase, the enzyme that breaks down the amino acid phenylalanine, which is present in protein-rich foods, such as meat or fish [7], as well as aspartame, a commonly used artificial sweetener. Because individuals with PKU cannot break down phenylalanine, toxic levels of the amino acid build up in their blood when they eat foods with phenylalanine, causing neurological damage. Guthrie’s niece had been diagnosed with PKU several years before.

Warner asked Guthrie for help to develop a simple and inexpensive method to diagnose individuals with PKU. To test his patients for PKU, Warner had to ship venous blood samples to California to determine whether or not the blood had higher than average levels of phenylalanine. At the time, a standard test for PKU was the ferric chloride urine test, which detected the presence of a phenylalanine in urine samples. Phenylalanine was present in urine of those with PKU because their bodies couldn’t decompose phenylalanine. Guthrie agreed to help Warner and reported a few days later that he had developed a new method to replace the ferric chloride urine test.

Guthrie’s method to diagnose individuals with PKU was a bacterial inhibition assay. Bacterial inhibition assays are tests that detect the presence of a specific substance in a sample. Guthrie’s test required a few drops of blood from a finger prick. To conduct the bacterial inhibition assay, Guthrie coated agar culture gel, a substrate used to grow bacteria, with β-2-Thietylalanine, an amino acid that inhibits the growth of the bacteria Bacillus subtilis [8]. Then, he collected a spot of blood on a filter paper disc and placed the disc on the surface of the agar culture gel. The presence of the amino acid phenylalanine in the blood, an indicator of PKU, reversed the inhibitory effects of β-2-Thietylalanine, causing B. subtilis to grow. Thus, a culture from an individual with PKU would show bacterial growth, while a culture from an individual without PKU would not.

After developing his test for PKU, and with a mentally disabled son and PKU-affected niece, Guthrie pushed for mandatory nationwide newborn screening of PKU. However, before every infant could undergo the Guthrie test for PKU diagnosis, the test had to go through clinical trials to prove its safety and efficacy. Near Rochester, New York, Guthrie tested his method on about 3,000 residents of a state school for the mentally disabled. His test detected twenty-three cases of PKU when the traditional test detected only nineteen cases. Thus, Guthrie showed his method was not only simpler and more convenient, but also more accurate than the traditional urine test.

After validating his test for PKU, Guthrie traveled the world to campaign for universal screening of PKU in infants. In 1960, Guthrie attended the International Association for Scientific Study of Mental Deficiency in London, England, where he introduced his PKU test. Guthrie also became involved in the International League of Societies for Persons with Mental Deficiency, which hosted a symposium for scientist studying mental disabilities. In 1961, the US Children’s Bureau in Washington, D.C., which worked to improve the overall health and well-being of the nation’s children and families, funded a trial to test Guthrie’s technique on 400,000 infants nationwide. Guthrie assembled warehouses to produce test kits and distributed them to twenty-nine states that agreed to use the test. In two years, thirty-seven cases of PKU were diagnosed in the group of 400,000 infants tested, an incidence of about one per 10,000.

In 1962, Guthrie presented his PKU test at the International Association for Pediatrics in Lisbon, Portugal. Guthrie traveled to Spain, Japan, and New Zealand, among other places, to introduce his PKU test. In the US, Massachusetts was the first state to mandate the newborn screening for PKU in 1963. However, many scientists opposed Guthrie and his test, claiming that the test was inaccurate. In 1963, an article in The Atlantic Monthly argued that Guthrie and Warner should be prosecuted for wrongly diagnosing infants with PKU. Guthrie’s test received acceptance among many scientists after Guthrie and his colleague Ada Susi published an article in Pediatrics about the Guthrie test in 1963.

In 1964, Guthrie further simplified his test so that infants could be screened at birth. He developed what he called Guthrie cards, pieces of cardstock on which physicians collected blood directly from a small heel puncture in the infant. Guthrie cards enabled doctors to save the dried blood samples of newborns for testing, hole punch them out, and place them onto the gel cultures for screening. Once the punched out discs holding dried blood were placed on the gel cultures, lab technicians performed the Guthrie test, watching for bacterial growth as an indicator of PKU. The convenience of Guthrie cards enabled doctors to diagnose in newborns so that the newborns could avoid ingestion of phenylalanine and prevent any damage to their body. By 1966, most states in the US mandated Guthrie’s newborn screen for PKU, while Guthrie attempted to develop additional tests to prevent mental retardation [8].

After developing and marketing his PKU test, Guthrie developed newborn tests for galactosemia and for maple syrup urine disease also using bacterial inhibition assays. Galactosemia is a disorder in which the body cannot metabolize galactose, a
sugar primarily part of lactose, leading to life-threatening symptoms such as lethargy, jaundice, liver damage, and abnormal bleeding. Maple syrup urine disease is an inherited disease in which the body cannot process specific amino acids, and it causes a sweet odor in the infant’s urine and developmental delays. If untreated, maple syrup urine disease can lead to seizures, coma, and death. Eventually, Guthrie’s laboratory developed tests for more than thirty different treatable conditions that cause mental disabilities or death. Guthrie’s grant for the PKU test from the US Children’s Bureau was extended until 1968 to test his other tests and add them to the list of routine newborn screens.

In 1975, Guthrie became a consultant for the California Department of Health in Sacramento, California. There, he urged for the investigation of lead poisoning in children. The Sonoma State Hospital in Eldridge, California, an institution for the mentally disabled, found a serious problem of lead poisoning. After that finding, Guthrie persuaded the Centers for Disease Control in DeKalb County, Georgia, to lower the maximum level of lead in the blood that was considered safe from 30 milligrams per 100 milliliters to 10 milligrams per 100 milliliters.

In the early 1970s, Guthrie also supervised the research of two scientists working in his laboratory, William Murphey and Adam Orfanos, who tested dried-blood spot specimens from residents of the West Seneca Developmental Disability Center in Buffalo, New York. Murphey and Orfanos found high levels of lead in the residents’ blood samples. Guthrie contacted the Newark Institution for the Mentally Retarded in Newark, New York, because the residents had earlier lived at that institution. After an investigation, the institution found lead-based paint in the Newark Institution. Consequently, New York State facilities were all tested for lead-based paint and, if necessary, repainted to prevent possible damages in residents from exposure to lead.

Toward the end of his life Guthrie also participated in Physicians for Social Responsibility, an organization that actively opposed nuclear weapon testing. Guthrie served as vice president and later president of the National Association for Retarded Children, Eric County chapter in New York. Throughout his life, Guthrie improved public schools by adding special classes for the mentally disabled and worked to educate the public about the dangers of lead poisoning. Guthrie died on 24 June 1995 in Seattle, Washington.

Sources


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