

Josef Warkany (1902-1992)

Josef Warkany studied the environmental causes of birth defects in the United States in the twentieth century. Warkany was one of the first researchers to show that factors in the environment could cause birth defects, and he helped to develop guidelines for the field of teratology, the study of birth defects. Prior to Warkany's work, scientists struggled to explain if or how environmental agents could cause birth defects. Warkany demonstrated that a deficiency or excess of vitamin A in maternal nutrition could cause birth defects. He also established that mercury in teething powders increased infant mortality rates. Warkany showed how substances outside the human body could adversely affect conception, growth, and development of the human fetus in utero.

Warkany was born in Vienna, Austria, on 25 March 1902 to Hermine Warkany and Jacob Warkany. Warkany had one brother and one sister. His father and brother served in the military during World War I, and while they were serving, Warkany recalled his family starving. After the war, he attended medical school at the University of Vienna in 1920 and received his medical degree in 1926. From 1926 to 1927, Warkany conducted a one-year residency at the University of Vienna Pediatric Clinic under the supervision of Clemens von Pirquet, who worked in immunology. Until 1931, Warkany was an assistant at the Reichsanstalt für Mutter und Säuglingsfürsorge (Public Institution for Mother and Infant Welfare) in Vienna, Austria. Warkany attended patients and studied calcium-phosphate metabolism and the biochemistry of tubercle bacillus (*Mycobacterium tuberculosis*), the bacterium that causes tuberculosis, with Hans Popper, a liver pathologist.

In 1932, Warkany left Vienna to study under Albert Graeme Mitchell during a one-year fellowship at the Children's Hospital Research Foundation in Cincinnati, Ohio. That year, the Foundation provided Warkany an assistant professor position at the University of Cincinnati College of Medicine in Cincinnati, where he managed an outpatient endocrine clinic. Often children with congenital malformations were referred to the clinic. In the clinic, Warkany met Suzanne Buhlmann and the two married in 1937. Together they had two children, Joseph Henry and Stephen Ford. In 1944, Warkany published a paper detailing that if pregnant women had poor diets, their infants could have birth defects. Warkany was promoted to associate professor in 1945, and to full professor in 1953. Warkany also worked as a pediatrician at the Children's Hospital and at the Cincinnati General Hospital.

During his early years in Cincinnati, Warkany and his colleague Rose Cohen Nelson showed that environmental factors such as dietary deficiencies in pregnant females could cause birth defects in their developing embryos. Warkany and Nelson observed vitamin D-deficient pregnant female rats. The offspring of those rats usually had retarded growth and shortened limbs, showing the influence environmental agents and substances or lack there of could have on developing fetuses. Warkany credited his inspiration for the experiment to his experience as a teenager during World War I while visiting remote valleys of Austria, where he noted that women who suffered from iodine deficiencies often had children with dwarfism.

Warkany's studies focused on congenital malformations, an area that was still developing. Prior to the 1940s, many scientists claimed that due to the protection of the placenta, mammal embryos could not be negatively impacted by external factors such as drugs and viruses. In 1940, Warkany published a series of reports challenging that claim. A year later in Australia, Norman McAlister Gregg discovered the rubella virus's ability to cause congenital cataracts in infants. That discovery strengthened Warkany's reports.

Warkany's experiment with vitamin-D deficient female rats sparked his three-decade-long career in teratology, and he focused primarily on birth defects caused by nutritional excesses and deficien-

cies. In particular, Warkany investigated the teratogenic potential of vitamin A in pregnant rodents. Working with colleagues in Cincinnati, Elizabeth Schraffenberger and James G. Wilson, he studied the teratogenic effects of feeding pregnant female rats diets deficient of vitamin-A. The offspring of those rats had heart and eye defects. Warkany's experiments showed the importance of maternal nutrition in fetal development and the need for a diet with adequate levels of vitamin-A. Years later, Warkany studied how too much vitamin-A in pregnant rats affected their offspring.

In 1948, Warkany and colleague Donald Hubbard in Cincinnati, determined a cause of pediatric acrodynia, also called pink disease. Infants with pediatric acrodynia can have pink hands and feet, a loss of teeth, increased blood pressure and pulse rate, hair loss, itching, and premature death. Warkany and Hubbard showed that pediatric acrodynia was caused by mercury intoxication from teething powders, ointments applied on the mother's nipples, and other similar products that contained calomel (mercurous chloride). Warkany discovered the toxicity of teething powders containing mercury when he requested urine tests for his patients with acrodynia. Though Warkany suspected arsenic or thallium poisoning to be the cause of acrodynia, the tests returned negative results for those two metals. The urine tests came back positive for mercury, leading Warkany to conclude that infants exposed to mercury in calomel-containing medications developed acrodynia. Some physicians were reluctant to accept Warkany's findings, but calomel was removed from teething powders and the incidence of pink disease declined sharply.

During the 1950s, Warkany continued to the study and treatment of birth defects. In 1950, Warkany worked with the National March of Dimes in White Plains, New York, to fund the prevention of birth defects. In 1956, Warkany founded the Hamilton County Diagnostic Clinic for the Mentally Retarded, which later became the Cincinnati Center for Developmental Disorders, in Cincinnati, Ohio.

Warkany's publications in the late 1950s reviewed research in experimental teratology and emphasized the importance of nutritional studies to explain the effects chemicals may have on offspring. In those articles and subsequent works, such as his 1965 *Teratology: Principles and Techniques*, co-authored with Wilson, Warkany detailed teratological principles such as the importance of dosage and observing the severity of defects in addition to their type and quantity. He also noted limits in using research on rodents to predict the effects of teratogens in humans.

Throughout the 1950s, Warkany and his colleague Wilson organized and held a number of teratology meetings for researchers. In May of 1954, the pair sent questionnaires to twenty-one scientists in North America to gauge interest in promoting teratology and in officially convening as a society. Researchers responded affirmatively, and after chairing a number of successful teratology conferences between 1956 and 1960, Warkany became the first president of the newly formed Teratology Society in 1960. Financial support came from the Human Embryology and Development Study Section of the US National Institutes of Health in Bethesda, Maryland, and the Association for the Aid of Crippled Children in New York City, New York.

On 26 May 1961, Warkany held the first annual meeting of the society at the Children's Hospital Research Foundation in Cincinnati, Ohio. Together with other members of the Teratology Society, Warkany contacted researchers in multiple countries to develop guidelines for the conduct of teratological studies. Prior to 1960, government agencies had not created guidelines for using animal studies to assess human teratological risks from drugs, environmental chemicals, or radiation. Additionally, although researchers had studied drug and product safety on children and adults, they had seldom analyzed what occurred to the offspring of pregnant animals exposed to the substances. The Teratology Society and its members planned to remedy the lack of guidelines by increasing communication between researchers studying birth defects.

At the University of Cincinnati in 1961, Warkany, along with Berry Monroe and Betty Sutherland, published a paper in which they distinguished between prematurity and intrauterine growth retardation. At the time, all infants born weighing less than 2,500 grams were labeled premature, regardless of their gestational age. Warkany and his colleagues noted that some infants labeled premature were not delivered prematurely and instead underwent growth retardation in the womb. Warkany identified exposure to radiation and nutritional deficiencies as possible causes of intrauterine growth retardation.

Warkany also showed the negative effects of ingesting too much vitamin-A in the early 1960s. In research published with a collaborator in Cincinnati, Harold Kalter, Warkany gave ninety-two pregnant female mice high doses of vitamin-A at different days after conception. The offspring had birth defects such as spina bifida, cleft palate, and eye defects. Warkany's studies with vitamin-A showed that substances from the environment could penetrate mammalian embryos to cause congenital malformations. As Warkany could explain how too little of a substance such as vitamin-A or too much of it could cause birth defects, he helped to establish safe doses to prevent pregnant women and their developing fetuses from facing preventable harm.

Warkany's research in the 1960s, along with other researchers' work on the causes of birth defects, helped expand the field of teratology. In 1960, thalidomide, a drug used to treat morning sickness in pregnant women, was recognized to cause birth defects such as missing or shrunken limbs. Prior to 1960, the medical community posited that congenital diseases were almost completely genetic with the exception of those that resulted from radiation, rubella (German measles), or vitamin deficiencies. The thalidomide case brought attention to the study of teratology that led to Warkany consulting for both health agencies and drug manufacturers.

In addition to birth defects, Warkany investigated factors leading to mental disabilities. In 1965, Warkany helped to obtain federal funds to establish the Institute for Developmental Research in a new building added to the Cincinnati Children's Hospital Research Foundation. Warkany directed the Institute until 1976. In 1977, he wrote a history of teratology. In 1981, Warkany published research about how mental disabilities in offspring were caused by tumors or by birth defects to the nervous system, such as abnormally small heads (microcephaly). Later in his career, Warkany consolidated information about birth defects into comprehensive publications.

Throughout his career Warkany received many awards for his contributions to general pediatrics, mental disorders, and birth defects. Some of those awards include the Modern Medicine Award for Distinguished Achievement in 1964, the Academy of Pediatrics Howland Award in 1970, the Charles H. Hood Foundation Award in 1972, the American Association on Mental Deficiency Research Award in 1976, the Procter Medal Award for Distinguished Research in 1979, and the March of Dimes Basil O'Connor Award in 1986. He published the results of over 200 investigations, half of which were published only after he retired in 1981. Warkany was also an artist, focusing on etchings and water colors. He displayed his works in individual shows and as part of group shows that traveled throughout the country.

On 22 June 1992, Warkany died of a stroke at the age of ninety in Scarlet Oaks Retirement Community in Clifton, Ohio.

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