



Editorial

The unwavering doctor who unraveled a medical mystery



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"An ailment which has baffled medicine for centuries has at last been relegated to the curable diseases"

[New York Times, 1938]

Diarrhea, dementia, dermatitis, and death are the signature 4 Ds of the now rare entity known as pellagra. Pellagra was once a national epidemic that baffled doctors and researchers. Between 1906 and 1940, approximately three million Americans developed pellagra, with 100,000 of these cases fatal (Rajakumar, 2000). Initially, the disease was believed to be a type of food poisoning that was caused by corn, and it took more than 30 years and one unwavering doctor to unravel the mystery of pellagra. (See Figs. 1 and 2.)

Pellagra was not recognized in the United States until the early 20th century. In the post-Civil War South, the Southern economy was almost exclusively dependent on the cotton industry. There was high pressure to grow cotton, which left little land for farming and livestock. The prevailing poverty of tenant farmers led to an impoverished corn-based diet for sustenance. In 1902, the first reports of pellagra surfaced from Georgia, followed by a pellagra outbreak in an Alabama asylum in 1906. The public reacted with panic, and a 1910 news headlines read "Musty cornmeal gave dreaded disease to family" (Wilkes-Barre Times-Leader, 1910) and "If you fear pellagra, beware of corn" (New York Times, 1909). In 1908, Public Health Services began to study the disease, and the Illinois Pellagra Commission concluded that pellagra was caused by a microbe.

Patients with pellagra were often identified by telltale skin signs: dry, scaly erythematous skin rash that would later peel and form oozing blisters, scabs, and crusts on sun-exposed areas (e.g., dorsum hands, feet, anterior V-neck, and across the cheeks). Patients with pellagra

also experienced stomach pain, nausea, vomiting, and foul-smelling diarrhea. At more advanced stages, the tongue and mouth would burn, which further inhibited nutrition. The symptoms were cyclical and typically presented in the spring. The symptoms would return annually and worsen with each occurrence.

Patients who were severely affected became depressed, confused, and anxious. Hallucinations often triggered an admission to a psychiatric hospital, and insanity was quickly followed by death. Knowledge of pellagra spread and caused those who were sick to be shunned and ostracized (Rajakumar, 2000). Some affected individuals took their lives to avoid the feared insanity. Mental institutions became flooded and overwhelmed with affected patients (Cavanna et al., 2013).

The Thompson-McFadden commission of 1912 and 1913 in Spartanburg County, South Carolina, found no connection between diet and pellagra and concluded that pellagra was an infectious, contagious, intestinal disease (Mooney et al., 2014). The commission implicated dirty outhouses or insects as the cause of spread of pellagra (Jarrow, 2014). However, the numerous doctors and public health officials who were assigned to study pellagra failed to determine its cause.

Pellagra was described as "the greatest riddle of the medical profession" and "a sphynx of which we have asked a reply and gotten none for nearly 200 years" (Kraut, 2003). The surgeon general turned to Dr. Joseph Goldberger, an infectious disease specialist, to head the pellagra investigation because he had previously cracked unsolvable cases in a matter of days. "You are preeminently fit for this work," the surgeon general wrote in a letter to Dr. Goldberger, and put him in charge of "one of the knottiest and most urgent problems facing the Service" (Goldberg papers, 1914).

Dr. Goldberger was born in the Austro-Hungarian Empire and immigrated with his family to the United States in 1883 when he was 9 years old. He graduated with honors from Bellevue Medical College in 1895 and worked at a general medicine private practice before joining the Public Health Service in 1899 (Markel, 2003). His first assignment was to examine immigrants at Ellis Island for signs of infectious diseases such as tuberculosis (Lowenstein et al., 2015). Over the next 12 years, Dr. Goldberger moved from one assignment to the next and thrived on solving challenging cases, which were often hazardous. He contracted yellow, dengue, and typhoid fever during the course of his assignments (Markel, 2003).

Dr. Goldberger had never seen a case of pellagra, so he read all pertinent literature he could get his hands on. Within a few months of studying, Dr. Goldberger made the observation in Southern mental hospitals, orphanages, and cotton mill towns that malnourished individuals developed pellagra, but those who were well fed did not. Dr. Goldberger became convinced that pellagra was related to the three Ms of the poverty diet: meal (corn), meat, and molasses



Fig. 1. Dr. Joseph Goldberger.

(Middleton, 2008). Within months of the start of his investigation, Dr. Goldberger said: “The disease impressed us as an intoxication rather than an infection” (Kraut, 2003).



Fig. 2. Alcoholic man with pellagra.

Dr. Goldberger made many observations, such as that the cyclical in the presentation of the condition was related to the end of the winter months when families ran out of money and subsisted on a more limited diet of the 3Ms. With increased sun exposure in the spring, skin manifestations developed. Women were at a greater risk than men, especially during the menstrual years when their bodies experienced increased nutritional demands. Men who rolled/chewed tobacco were somewhat protected; subsequently, tobacco was found to be a source of vitamin B. Black individuals, who were generally more impoverished, were at greater risk than white individuals, at a ratio of >2:1 (Vasilev and Vulkov, 1958).

Despite Dr. Goldberger's careful observations, he experienced resistance from both physicians and the public. He orchestrated an experiment to induce pellagra by providing a nutritionally deficient diet. The Mississippi governor volunteered inmates of the Rankin prison farm and offered them pardons upon completion of the experiment (Jarrow, 2014). The group of inmates, who were called The Pellagra Squad, ate a diet of corn grits, pork fat, and syrup with small amounts of vegetables such as sweet potatoes and collard greens (Jarrow, 2014). At the end of the 6-month trial, 6 of 11 prisoners had developed pellagra (Jarrow, 2014). Some physicians criticized his study methods and remained skeptical. Moreover, Southern doctors took offense to the connection between pellagra and poverty in the South (Jarrow, 2014).

Dr. Goldberger devised another experiment to discredit his critics once and for all. He attempted to infect himself with pellagra by using skin, scales, feces, urine, blood, saliva, and other body fluids taken from pellagrins, which he would form into a pill. Dr. Goldberger, his wife Mary, and other volunteers organized “filth parties,” where they consumed these pills and injected themselves with the blood of infected patients (Jarrow, 2014). None of the party attendees developed pellagra. Despite his discoveries, the statistical studies that Dr. Goldberger conducted were unwelcome and went unheeded.

By 1916, a total of 100,000 cases of pellagra were reported in 13 states. A dramatic drop in cotton prices in 1920 and the attendant decrease in the income of many Southerners occasioned a spike in the number of reported pellagra cases (Jarrow, 2014). Dr. Goldberger publicly predicted dire public health consequences for 1921, and he was correct. He advocated for social reform, citing poverty and the land tenure system as the source of the problem. This outraged people of the South. Southern doctors embraced the moldy corn theory in opposition to his conclusions and were indignant about accusations of the maltreatment of black patients, who were more significantly affected (Jarrow, 2014).

Although Dr. Goldberger felt confident, his work was largely ignored, and the death toll from pellagra continued to rise. During the 1920s, Dr. Goldberger identified a pellagra preventive factor: a daily dose of brewer's yeast cleared patients of pellagra. In 1927, he tested his hypothesis on 50,000 survivors of the Mississippi River Flood. The survivors were fed brewer's yeast by the Red Cross, and all affected individuals were cured within weeks (Jarrow, 2014).

In 1929, Dr. Goldberger suddenly became ill and died from kidney cancer (Markel, 2003). He had devoted 15 years of his career fighting pellagra and stated in 1928 that it is beyond a “reasonable doubt that pellagra is a vitamin deficiency disease” (Jarrow, 2014). In 1937, 8 years after Dr. Goldberger's death, researchers at the University of Wisconsin identified the exact cause of pellagra: a niacin deficiency (Jarrow, 2014).

Between 1907 and the early 1940s, pellagra affected >3 million individuals in the South, with >100,000 deaths (Rajakumar, 2000). By the 1950s, pellagra had nearly vanished, and although rarely seen today, pellagra continues to occur in the context of malabsorption (i.e., Crohn's disease; Hui et al., 2017), alcoholism (Luthe and Sato, 2017), malnutrition, (i.e., eating disorders) and exposure to certain medications (i.e., azathioprine, isoniazid; Zhao et al., 2018).

Dr. Goldberger's methods were not on par with today's standards for ethical investigation, including prisoners being coerced to participate with the promise of freedom and the infection of volunteers in the absence of institutional review. Still, the story of Dr. Goldberger's unwavering dedication and tenacious pursuit of the cause of pellagra saved and improved innumerable lives, and his work remains inspirational to this day.

Sarah Schmitz BS
SUNY Downstate College of Medicine, Brooklyn, New York
 Corresponding Author
Email address: sarah.schmitz@downstate.edu

Eve J. Lowenstein MD, PhD
Department of Dermatology
SUNY Downstate College of Medicine, Brooklyn, New York

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