

Joseph Goldberger: An Unsung Hero of American Clinical Epidemiology

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■ Pellagra, a disease rarely seen in developed countries today, was common during the first half of this century in the United States. The disease was initially believed to be infectious, and severe "pellagraphobia" left many victims and their families ostracized. This paper calls attention to Joseph Goldberger, an American physician whose remarkable research helped correct the erroneous belief in an infectious cause for pellagra and led to the elimination of pellagra epidemics in the United States.

Ann Intern Med. 1994;121:372-375.

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Asked to name one of the great heroes of epidemiology, many respondents today would probably cite John Snow, who not only identified contaminated water from London's Broad Street pump as the source of a cholera epidemic in 1854 but also arranged for the pump handle to be removed (1). Snow has received widespread veneration as a scientist-activist, and the London pub named after him is often the site of epidemiologic "pilgrimages." Joseph Goldberger (Figure 1) was also a scholarly, admirable, and bold scientist-activist, but he is generally forgotten today and is not even referenced in several textbooks devoted to public health epidemiology (2-4). In an age of vanishing heroes, his exploits deserve to be better known. His current neglect is probably due to social and political factors that interfered with prompt acceptance of his research findings.

Joseph Goldberger was born in 1874 and studied medicine at Bellevue Hospital Medical School in New York, graduating with honors in 1895. After an internship at Bellevue Hospital College, he engaged in private practice for 2 years and then joined the Public Health Service Corps in 1899. During routine work as a quarantine officer on Ellis Island, Goldberger rapidly acquired a reputation for outstanding investigative studies of various infectious diseases, including yellow fever, dengue fever, and typhus (5).

Goldberger devoted the latter part of his career to studying pellagra. After quickly contradicting the contemporary general belief that pellagra was an infectious disease, he spent the last 15 years of his life trying to prove that its cause was a dietary deficiency. His etiologic hypothesis created an embarrassing social and political problem, because the idea that pellagra was due to infection was more acceptable than the idea that the disease was caused by the malnutrition of poverty. During the

first half of this century, an epidemic of pellagra produced roughly 3 million cases in the United States, about 100 000 of which were fatal (6). That such a huge epidemic disease has quietly disappeared, with most physicians today having never seen a case, is quite remarkable and is in many ways due to Goldberger's work.

Background on Pellagra

Pellagra, which is caused by a dietary deficiency of nicotinic acid, is now relatively unknown in developed countries. The disease is clinically manifested by the "four D's": diarrhea, dermatitis, dementia, and death. Patients present initially with symmetrically reddened skin, similar to that produced by a sunburn or poison oak. The dermatitis turns rough and scaly in one or more locations, such as the hands, the tops of the feet, or the ankles, or in a butterfly-shaped distribution across the nose. Severe disturbances of the digestive tract and the nervous system are late manifestations. It has been suggested that the Biblical Job suffered from pellagra, not syphilis or leprosy (7).

Although only a few sporadic cases were known in the United States before 1906, pellagra rapidly spread after that date, becoming particularly common in the Southern states, among the poor, and especially among blacks. Reporting of pellagra was never complete; each state decided whether it would recognize and publicly admit the existence of what was then considered an embarrassing plague. The total number of new annual cases was estimated as about 75 000 in 1915 and as about 100 000 throughout the 1920s (6). The disease had a 40% mortality rate, and many survivors with dementia were confined to mental institutions (8). The epidemic in the United States lasted from about 1906 to 1940.

What provoked the epidemic is not clear. Changes in the methods of milling corn in 1901 might have led to the initial outbreak, because the germ or embryo in the corn kernel is removed in the milling process and contains a high proportion of lipid, enzymes, and cofactors, including nicotinic acid (6, 9). Pellagra was often called the "sharecroppers' plague," becoming prominent when tenant farming was used to maintain Southern agriculture after the abolition of slavery in the United States. Because the sharecroppers had to grow the landowners' crops, usually cotton, on every available inch of land, no space was available for growing vegetables or meat. The tenants, therefore, usually subsisted on the "three M's" available from the landowners' stores: meat (fatback), meal (corn meal), and molasses. The worse the economic status of the landlord, the greater the dependence on a single crop, and the more likely the maintenance of a sharecropping system (10).

Severe "pellagraphobia" developed as the disease ac-

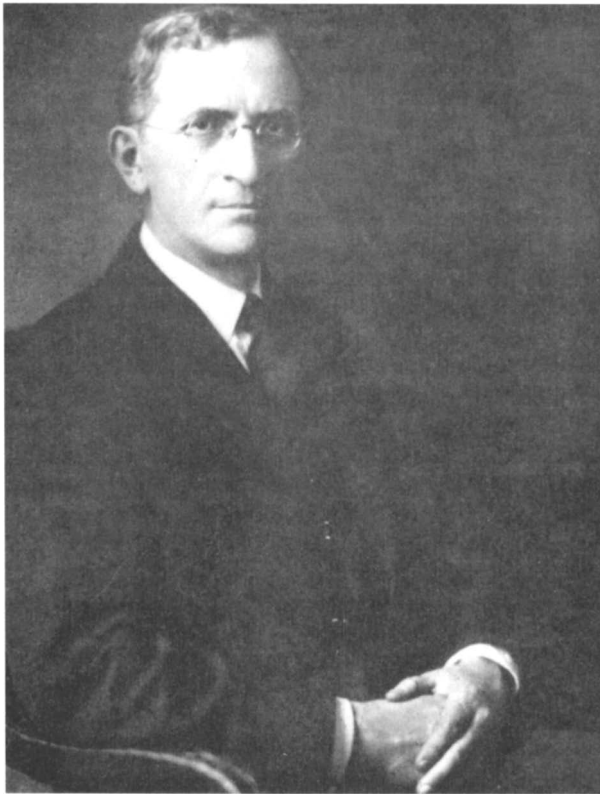


Figure 1. Joseph Goldberger 1874-1929. Reproduced from Terris (5) with permission from the Louisiana State University Press.

quired a social stigma akin to that of leprosy, which left many victims and their families ostracized (11). Many hospitals refused admittance to, and some hospital staff refused to care for, patients with pellagra; the patients were often quarantined; and elementary schools tried to bar children whose family members had pellagra (12). The disease aroused a plethora of unsubstantiated etiologic suspicions that included the eating of moldy corn; inherited susceptibility; emancipation of the slaves; heavy exposure to sunlight (because the dermatitis was noted most often in the spring); and exposure to cottonseed oil (because the disease frequently occurred among sharecroppers) (6). The more than 200 proposed "cures" for pellagra included diet, arsenic, castor oil, quinine, strychnine, and the healing waters of mineral springs (12).

This etiologic uncertainty appeared to be resolved after a study by the Thompson-McFadden Pellagra Commission, a group that had been established under governmental auspices and resembled the Surgeon General's commissions that began about 50 years later. However, unlike the Surgeon General's groups, which evaluate published literature, the Thompson-McFadden group did original research, conducting a house-to-house survey of pellagra cases in the cotton mill districts in South Carolina. In its 1914 reports (13, 14), the commission concluded that pellagra had no relation to diet, that it spread most rapidly where sanitary disposal of waste was poorest, and that the disease occurred almost exclusively in people who lived in or next to the house of another person with pellagra. The Commission's reports did not mention an association with poverty. In an era when infection was being sought and found as the cause of many other dis-

eases, the Commission's findings were interpreted as strong support for an infectious cause of pellagra.

Goldberger's Studies

Preliminary Observations and Hypothesis

In 1914, the U.S. Public Health Service assigned Joseph Goldberger to study pellagra, presumably to help find its infectious agent. Goldberger spent his first 3 weeks in the southern part of the United States, directly observing patients with pellagra and their living environment. Noting what others before him had looked at but not really seen, he summarized his observations with a report and hypothesis (15) that he spent the rest of his life demonstrating. Goldberger stated that pellagra was: 1) present almost exclusively in rural areas; 2) associated with poverty; 3) associated with a relatively cheap and filling diet consisting of the "three M's"; and 4) not acquired by nurses, attendants, or employees in hospitals or orphanages whose inpatients had the disease.

The last finding seemed particularly incompatible with an infectious cause for pellagra, because the attendant staff worked in close association with the inmates, and some even lived in the wards under the same conditions. Goldberger believed that the staff's peculiar exemption from or immunity to the disease could be explained by a difference in diet. At some institutions, the inmates and staff had a manifest difference in diet, but even when the diets were apparently similar, Goldberger noted that the staff could choose for themselves the best and greatest variety of foods.

Human Experiments

To prove his hypothesis, Goldberger tried to prevent and cure the disease with a dietary intervention in two orphanages having high rates of endemic pellagra (16). To ensure that the results would be attributed to dietary interventions rather than an absence of infectious causes, he insisted that sanitary conditions remain unchanged during the study. After finding 172 patients with pellagra and 168 children who were initially free of disease, he arranged for both groups of children to receive a new, more varied diet, subsidized by federal funds. The results were evident in just a few weeks: No new cases of pellagra occurred and almost all children with pellagra were cured. After a year, the two orphanages had only one case of recurrent pellagra.

Goldberger then repeated the study in a mental asylum, using both a treatment and a control group followed for 1 year (16). Of 72 patients with pellagra, all were cured after the introduction of the new diet. The treatment group had a high drop-out rate, however, because some patients' mental status improved so greatly that they were permitted to leave the asylum. In the control group, which was kept on the old "three M's" diet, the recurrence rate of pellagra was almost 50%. Goldberger was pleased by the striking results in the orphanage and mental asylum studies, but when the federal subsidies expired at the end of these studies, the diets returned to the old "three M's." By the spring of 1916, 40% of the inmates again had pellagra.

Persisting in his efforts, Goldberger then began a new study intended to induce pellagra by dietary deprivation (17). In a prison where pellagra had never been reported, Goldberger chose a dozen volunteers for what he called the "pellagra squad." These volunteers were promised full pardons at the experiment's end. This study would probably not receive institutional review board approval today. At the time of Goldberger's work, however, some of our modern legal and ethical principles had not yet been developed, and conducting research on prisoners was a common procedure.

During the prison experiment, the volunteers lived in particularly clean, commodious quarters, carefully screened from insects and other carriers of disease. The experimental diet, which was common in the South, consisted largely of cereal and included biscuits, gravy, cornbread, grits, rice, syrup, collard greens, and yams. The ill effects of the diet appeared in 1 inmate in 2 weeks, and, by the end of the 9-month study, 6 of the other 11 inmates had an incontrovertible diagnosis of pellagra. In all instances, resumption of a better diet resulted in cure. A few of the volunteers tried to end the experiment prematurely, one saying, "I have been through a thousand hells!" Goldberger was accused of torture, and the state's Governor was accused of arranging the whole experiment in order to pardon 2 prisoners, convicted of embezzlement, who were his friends. Skeptics remained unconvinced that pellagra was not infectious (12).

In a further effort to refute the theory that pellagra was infectious, in 1916 Goldberger developed a program that he called "filth parties" (18). He injected blood from patients with pellagra into the deltoids of 16 healthy volunteers, including himself and his wife. He also mixed extracts of skin parings, nasal secretions, urine, and feces from patients with pellagra into a wheat dough concoction that was swallowed by all volunteers. These "filth party" experiments were repeated seven times. Although many participants developed diarrhea and nausea, no signs of pellagra were ever noted. These studies, however, were also dismissed by proponents of the infectious cause, who argued (among other things) that because pellagra was more common in women, the 15 male participants in these studies must have been "constitutionally resistant" to the disease.

Community Studies

Because the general public was not persuaded by evidence from selected groups of subjects, in 1918 Goldberger undertook field surveys of seven cotton-mill villages (19, 20) to get more information on the basic demographics, socioeconomic status, and diet of patients with pellagra. These surveys differed in important methodologic ways from previous field investigations. First, the diagnosis of pellagra depended on the inspection of all village households by a physician making home visits at 2-week intervals. Second, dietary data were obtained for 6 months immediately before the period of expected high incidence of disease (previous investigators had looked only at the association of current diet and disease). Third, the dietary data were obtained objectively, from a 15-day recording of all household purchases.

In these surveys, Goldberger found that an unprofitable

year in cotton production was usually followed by an increase in the incidence of pellagra and pellagra mortality, and vice versa (20). Using a socioeconomic unit developed to measure variation in gross demands for consumed materials, Goldberger and his colleagues showed a significant relation between this socioeconomic unit and the incidence of pellagra. They also found a significant correlation between the rise and fall in the price of animal protein foods and the disease's onset and remission (19, 20). With these data, Goldberger believed the association between pellagra and a dietary deficiency was unequivocal.

Laboratory Studies

For Goldberger's final work, he abandoned the epidemiologic method, believing that it had confirmed his original hypothesis and had reached the limits of its own potential. Uncertain about which part of the diet cured or prevented pellagra or which dietary deficiency caused the disease, Goldberger turned to the laboratory and worked with an animal model of the disease (21). He hypothesized that the disease was caused by an amino acid deficiency, possibly that of tryptophan, which he called the pellagra-preventive factor (5).

Goldberger soon realized that ordinary yeast contained and seemed to be the most potent source of the pellagra-preventive factor (22). In 1927 he arranged to have the Red Cross ship large quantities of yeast into flood-stricken areas along the Mississippi river (23). The expected outbreak of pellagra did not occur; instead, the disease fell below its usual seasonal incidence. After the emergency, yeast was no longer provided, and the usual level of pellagra returned to the area. Goldberger died in 1929, before he could complete his laboratory research or find a specific clinical cure.

In the end, Goldberger's intuition about tryptophan turned out to have a basis in metabolic fact. In 1937, Elvehjem and colleagues (24) showed that nicotinic acid cured canine black-tongue, the animal model of pellagra. This finding was immediately confirmed for human pellagra, and nicotinic acid was shown to be the pellagra-preventive factor that Goldberger had postulated. Furthermore, work since 1945 has shown that the amino acid tryptophan is converted to nicotinic acid in humans as well as in many species of animals (25). The availability of inexpensive, synthetic forms of various vitamins subsequently led to legislation in many states requiring that vitamins be added to commonly used foods (26). The final, almost complete elimination of pellagra dates to the 1940s.

Politics and Pellagra

As are many episodes in the history of medicine and public health, Joseph Goldberger's story is interwoven with national, social, and economic events. Goldberger had innocently stumbled in 1914 into the politics of hunger and poverty in America—a thorny issue that has still not disappeared. He did not realize that years of experimental work, assiduous public health campaigning, astute diplomacy, and political skill would be needed to persuade the public, the medical community, and the politi-

cians that pellagra was associated with poverty and a poor diet.

Because pellagra had rapidly reached epidemic proportions at a time when all epidemic diseases were thought to have a microbial cause, thinking about the etiology was directed toward an infectious agent. Causative agents (and a few distinct insect vectors) were being discovered at the rate of about one disease per year for entities such as cholera, malaria, scarlet fever, tetanus, typhoid fever, lobar pneumonia, tuberculosis, syphilis, and diphtheria.

The Southern United States, still sensitive from the "lost cause" of the Civil War a half-century earlier (6), was affronted by the reported concentration of pellagra in the South and by its association with poverty. Southern sensitivities were further riled when social and economic factors were indicted in research done by Goldberger, a Northerner (6).

In a letter to the Surgeon General, Goldberger described the extent of pellagra and its relation to poverty and poor diet. After this letter reached the press, President Warren Harding was stimulated to urge that the Red Cross provide aid, and to suggest a special congressional appropriation request. The attendant publicity again offended Southern pride. One Southern congressman, calling for rejection of offers of aid, said the news reports of "famine and plague" in South Carolina were an "utter absurdity" (12). Residents of a Georgia city, in a telegram to their senator, said "When this part of Georgia suffers from famine, the rest of the world will be dead!" (12) The United Daughters of the Confederacy at first voted to thank President Harding for his concern, but a month later the group sent him a letter of protest (12).

Pellagra eventually disappeared, probably not because of direct nutritional interventions or supplements, but because of social and economic changes. These changes occurred when cotton production was reduced by economic depression, soil erosion, outdated methods of agriculture, and the ravages of the boll weevil. Especially during the Great Depression, southern farmers stopped planting cotton and began to diversify the use of their land, thus leading to a more varied diet.

Conclusions

Joseph Goldberger's story is not unusual in showing the delay between pioneering medical discoveries and effective public policy. At least 50 years elapsed before James Lind's demonstration of a citrus-juice cure for scurvy was converted into routine "lime" supplements for the British navy (27). A long and fierce set of political battles was fought before the "sanitary movement" of the latter 19th century could transform John Snow's discovery into suitable improvements for disposal of sewage and purification of water (28).

What is unusual about Goldberger is his relative obscurity in his native land and the extraordinary breadth of his research. In today's environment, a single investigator would probably be unable to move as gracefully as Goldberger from community observation to clinical experiment to the laboratory bench, producing excellent examples of both public health research and clinical investigation in disease. As a masterpiece of investigative craftsmanship, these extraordinary accomplishments surely warrant better

recognition for Goldberger as an American hero in the scientific pantheon of both public health and clinical epidemiology.

Acknowledgements: Dr. Elmore was a Robert Wood Johnson Clinical Scholar when this paper was written.

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