From the Editor
Pellagra, Osler, Roberts, Goldberger, the Atherosclerotic Diet, Niacin, the Beginning of the Atherosclerotic Epidemic, and the First Lipid-Altering Drug

William Osler (1849 to 1919) in 1892 published *The Principles and Practice of Medicine* (1). Under the heading "grain poisoning" Osler devoted just over one-half page in the 1,079-page book to Pellagra. He described it this way:

> "This is a nutritional disturbance due to the use of altered maize. The disease occurs extensively in parts of Italy, in the south of France, and in Spain. It has not been observed in this country. It prevails extensively among the poorer classes, particularly in the country districts and appears to be associated in some way with the use of maize which...is fermented or diseased. In the early stage the symptoms are indefinite, characterized by debility, pains in the spine, insomnia, digestive disturbances, more rarely diarrhea. The first clear manifestation of the disease is the pellagral erythema, which almost invariably appears in the spring. This is followed by desiccation and exfoliation of the epidermis, which becomes very rough and dry and occasionally crusts form...with these cutaneous manifestations there are digestive troubles − salivation, dyspepsia and diarrhea − which may be of a dysenteric nature. After lasting for a few months, improvement occurs in milder cases and convalescence is gradually established. In the more severe and chronic forms there are "pronounced nervous symptoms − headache, backache, spasms, and finally paralysis and mental disturbances..."

In 1912, my father, Stewart R. Roberts (1878 to 1941), published a 272-page book entitled "Pellagra: History, Distribution, Diagnosis, Prognosis, Treatment, and Etiology" (2). The book was dedicated as follows:

> "To that long line of physicians and scientists from Casals, through Lombroso to Sambon, and those who shall come after them who have been and are and shall be students of pellagra, with the hope that the day is not far distant when there shall arise from among them one to whom shall be revealed with clear and certain proof the true cause of the Mal de la Rosa."

Because the disease was so common in Italy, Dr. Roberts spent some time seeing patients and touring institutions in Italy in preparation of his book. In Chapter 10, he reviewed the various theories as to the cause of pellagra and he emphasized that its cause at that time was unknown. He reviewed the intoxication and infectious theories, the 2 major hypotheses at the time. The chapter on Cause was the last one in his book and the chapter on Treatment of Pellagra was chapter 9. He wrote:

> "The first step to the treatment of pellagra is to ascertain whether any other disease is present...pellagra is disease enough for any patient to have at one time. Its draining and resistance-lowering powers increase the capacity of any associated infection or disease to do greater damage. Pellagra affords fight enough to test the strength of the patient and the skill of the physician. Any other disease increases the danger and lessens the chance of improvement from treatment. Pellagra acts as an alarm clock to awaken a sleeping infection. The pellagrin should be examined for tuberculosis, intestinal parasites, and malaria, and syphilis is not to be forgotten. The feces should be examined for amebae and especially for hookworm ova, and occasionally other ova...In the South a latent malaria or hookworm infection is chiefly to be expected and associated infection...there is no drug which cures pellagra."

> "The pellagrin should be on as generous and as nutritious a diet as is compatible with his powers of digestion and the condition of his alimentary tract. His strength is to be conserved and his diet is to him both a food and a stimulant. When the attack is at its height, the mouth raw and sore, solid food cannot be taken. Even acid liquids−as orange juice, orange and lemon albumen, and grape juice−give pain and are to be avoided. At this time soups or broths of the ordinary kind, milk, strained oatmeal, coffee, tea, malted milk, may be used...As convalescence begins, the liquid diet may be changed to a light diet, with the addition of mashed Irish potatoes, mashed sweet potatoes, boiled or scrambled eggs, butter, toast, scraped beef, rice with milk, and fruits...With continued improvement, the change from the light diet to a general diet may be made, with a continuance, so far as possible, of the nourishment between meals and bedtime. Added the articles already mentioned are meats, as broiled steak, roast beef, chicken, and fish. Hog meat is to be avoided...there is a demand on the part of his system for protein containing foods. In addition to the meat, eggs can be freely given and the lighter variety of cheese. Rice, hominy, the more easily digested vegetables−especially potatoes, English peas, Boston baked beans−are favorites at this time...Butter and fats are to be given in large quantities, and, as a rule, will be found to be digested easily. The pellagrin and his tissues demand proteins, carbohydrates, and fats, and his diet is to be as generous as his condition permits and as his digestion is good."

Two years after my father's book appeared, Dr. Joseph Goldberger (1874 to 1929), an ingenious epidemiologist and a fearless epidemic fighter, with the rank of surgeon in the US Public Health and Marine Hospital Service (USMHS) (later called Public Health Service) was assigned in February 1914 by Surgeon General Rupert Blue to take

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over the pellagra studies from Dr. Claude Lavinder, who had requested reassignment. The story of Goldberger's war against pellagra is beautifully described in a book entitled *Goldberger's War: The Life and Work of a Public Health Crusader* by Alan M. Kraut (3). The remainder of this piece comes from Kraut's wonderful book.

When 9 years of age, Joseph Goldberger immigrated with his family to the United States and settled in New York City in 1883. His father, Samuel Goldberger became a proprietor of a mom-and-pop grocery store in Manhattan. The family lived in the East Side tenements such that young Joseph grew up smelling the stench of urban poverty. The Goldbergers' saw education as the port of entry to American life and Joseph entered the College of the City of New York at the age of 18 (later named City College). He intended initially to become an engineer but after 2 years he left to become a student at Bellevue Hospital Medical College of New York University. A popular lecturer was Dr. Austin Flint, Jr., who had a reputation for exciting his classes. Goldberger received his MD degree in 1895, a month before his 21st birthday. He had scored high on his hospital examination and by October 1897, he had completed his 2-year internship at Bellevue Hospital. He then went into private practice, initially in New York City, and then in Wilkes-Barre, Pennsylvania. Goldberger found being a family doctor in a small city intellectually unfulfilling. In 1898, he tried to join the US Navy at the outbreak of the Spanish-American War, but the Navy rejected him. He then joined the USMHS (later changed to the US Public Health and USMHS and then to US Public Health Service). Between 1902 and 1914, Goldberger was a public health physician becoming an expert epidemic fighter. He battled yellow fever in Mexico, Puerto Rico, Mississippi, and Louisiana. He fought typhoid in Washington, D.C., dengue fever in Texas, and typhus in Mexico City. On 3 occasions Goldberger contracted the disease he was studying: yellow fever, dengue fever, and typhus. Later, he did research on measles and battled diphtheria. In 1914, Surgeon General Rupert Blue assigned him to supervise the federal government's pellagra investigation.

After being assigned to the pellagra mission in February 1914, Goldberger initially went to the library of the Hygienic Laboratory (later called the National Institutes of Health) and read everything he could about pellagra. The library closed at 10:00 pm and he was unable to remove books so on many occasions he brought a cot to the library so he could stay the night. By the time he had finished reading about the disease he believed it was not an infectious disease but was somehow related to diet. Rather than believing that there was some toxic substance in the food he was the first to believe that there was an essential substance absent from the food the pellagrin was eating.

The notion that eating certain foods prevented specific illnesses was known to Goldberger. As early as 1753, well before scurvy was fully understood as a deficiency disease, James Lynn had discovered that citrus fruit could prevent the condition. Similarly, beriberi was being successfully treated from extract of rice bran before anyone understood why it worked. As Goldberger pondered the relation of diet to pellagra others were wondering if the malformities of Rickets were not the result of a dietary deficiency also.

His homework completed, Goldberger boarded the train, one of the many he would be riding across the South in the months and years ahead. It had prepared himself to examine the telltale signs of pellagra on the bodies of the victims. He was anxious to visit institutions housing large numbers of pellagrins to observe how they lived and what they ate. Only then could he test his hypothesis that the pellagrin germ was a myth, that corn was not the culprit, and that the root cause of the scourge was in the diet. Goldberger now 40 years old, first stopped in Stanton, Virginia, where he visited several insane asylums in that state. From Virginia he went to Georgia, Alabama, Florida, and Kentucky, then back East to Columbia, South Carolina, and Atlanta, and on to New Orleans, and again to Alabama and then to Mississippi visiting asylums, orphanages, and prisons—places where pellagra frequently appeared. Everywhere he went he asked institution superintendents for data on the pellagra incidence, diets of inmates and staff, especially corn consumption, and permission to inspect sanitary conditions. As he had done in the alleys of Puerto Rico, Mexico, and Brownsville, Texas, he hunted for insects that might be carrying the disease from victim to victim. What struck Goldberger most was that in all the institutions he visited not a single staff member had pellagra. (No infectious disease selects victims by status!) In May 1914, he visited Jackson, Mississippi, and there encountered the orphanages that would become crucial sites for his studies. With his usual meticulous work habits, Goldberger wrote in his small notebook all that he knew up to that point about the orphans' home and what the youngsters ate at each meal.

In June 1914, Goldberger, for the first time, told the public health community what he believed about pellagra. In an article titled "The Etiology of Pellagra," he concluded that pellagra was not a contagious disease. This message came home when not in a single institution he had visited had a staff member who had gotten pellagra. The staff ate different diets than did the residents. He agreed with certain previous investigators that pellagra was generally a rural disease and one associated with poverty. He asked, however, what important difference there was between poverty in urban slums and those in rural areas? He believed that the very poor in cities had a more varied diet than the poor in rural sections. His suggestion for therapy was to improve the diet of the afflicted. Specifically, he called for a reduction in cereals, vegetables, and canned foods, and an increase in the fresh animal food component, such as fresh meat, eggs, and milk. Goldberger knew that he needed to test humans for his dietary hypothesis and that started in September 1914. To one group of orphans, he gave fresh meat, milk, and eggs, and to the other group, the diet of the institution. Although the orphan experiment was still in progress, Goldberger, confident that he knew the answer for pellagra, published another report entitled "The Treatment and Prevention of Pellagra" emphasizing his 3 preliminary conclusions: (1) that pellagra was not an infectious disease but a disease of dietary origin; (2) that is, was dependent on a still unknown fault in the diet in which the animal or leguminous protein component was disproportionately small and the nonleguminous vegetable component was disproportionately high; and (3) that no pellagra developed in those eating a mixed well-balanced and varied diet. He

emphasized that no pellagra was seen among the enlisted men—Army, Navy, and Marine Corps—for the World War I conflict. Based on these conclusions, Goldberger and his colleagues recommended that as long as clinical evidence of pellagra manifested, the patient should be given and urged to eat an abundance of fresh milk, eggs, fresh lean meat, beans, and peas. Milk, he described, as the most valuable single food. He urged adults to drink not less than a pint and a half to 2 pints each 24-hour. He recommended 4 eggs per day and fresh lean meat. He encouraged adults to take at least a half-pound of lean meat a day in addition to the milk, eggs, and legumes. He also recommended excluding corn. Not only did his diet offer a cure, a well-balanced varied diet rich in animal protein also was the best preventative of pellagra.

In December 1914, Goldberger was invited to Cambridge, Massachusetts, to give the prestigious Cutter Lecture on Preventive Medicine. He titled it "Diet and Pellagra." He began his presentation by explaining the enormity of the pellagra problem citing "not less than 50,000 cases" for 1914 with 11,000 in the state of Mississippi alone. He emphasized that "pellagra is essentially a rural disease and a disease of poverty." His data revealed that women were at a greater risk than men and that blacks at a greater risk than whites. In Mississippi in 1913, 56/100,000 blacks and 26/100,000 whites had died of pellagra. He emphasized that a pellagrin's diet was missing a substance, which could be found in animal protein foods—meat or milk or both. Goldberger emphasized that pellagra was due to a lack or deficiency of an animal-protein food, "a fault" brought about in some yet undetermined way in diets of a certain type (largely corn or other cereal or starchy food or combination of them) and that this fault was corrected or prevented by including in such diets a suitable portion of animal-protein foods. He also emphasized that the common legumes (beans and peas) were of value in this respect.

After returning to the field, Goldberger produced pamphlets describing how to prevent and to treat pellagra, and he distributed them in churches and stores and by mail. In Georgia alone, 80,000 pamphlets were circulated.

The orphanage experiences were coming to fruition. They began by treating the orphans under 12 years of age with a 7-ounce cup of milk twice a day and at least 1 egg a day. For those under 6 years, milk was prescribed 3 times a day. Meat was prescribed 3 to 4 times a week rather than once a week. Beans and peas were made part of every meal. Because Goldberger regarded the corn theory of pellagra as highly suspect he chose not to eliminate corn from the orphan's diets altogether. Cornbread was served once a week and grits were allowed for those over 12, once or twice a week. At one orphanage, 67 of the 79 pellagrins after 1 year of using the Goldberger diet had no signs of recurrence of pellagra. At the other orphanage, 105 of the 130 pellagrins had no evidence of a recurrence of pellagra at 1 year.

Nevertheless, Goldberger had to prove that the poor diet could produce pellagra. Together with the Governor of Mississippi and the Rankin State Prison Farm, a facility for white convicts about 8 miles from Jackson, Mississippi, Goldberger screened with the governor's permission and with full permission from each state prisoner, permission to give the deficient diet to produce the disease. Earl Brewer, the Governor of Mississippi, and Goldberger dangled the promise of pardons before approximately 80 inmates. The requirement was that the prisoner volunteer for 6 months eating the deficient diet. Among the 80 prisoners, Goldberger selected 12, half of them murderers serving life terms. The 12 convict volunteers were housed in what was commonly called "the new hospital building"—a small-screened one-story cottage away from "the cage" where the other inmates lived. Goldberger's volunteers were strictly separated from the other convicts to ensure they were not contaminated by personal contact with other inmates who might have pellagra or who might supply them with some foods. A typical breakfast included what Goldberger often saw in the asylum inmate: biscuits, fried mush, grits, brown gravy, cane syrup, and coffee with sugar. Lunch included cornbread, collards, sweet potatoes, grits, and syrup. Supper included biscuits, mush, rice, gravy, syrup, and coffee with sugar. This was the typical diet of cotton mill workers, sharecroppers, and tenant farmers. The entire inmate population of the "camp" was considered the control group and they all ate meat, drank milk, and, ate good vegetables daily, and none had any symptoms of pellagra. The diet started February 1, 1915, and ended October 30, 1915. The results of the Rankin Prison experiment were announced November 1, 1915. Six of the 11 men who finished the experiment showed clear evidence of pellagra. The evidence was confirmed by a number of outside physicians who examined the prisoners. Newspapers all over the country trumpeted Goldberger's demonstration that he could induce pellagra in strong healthy men by depriving them of fresh milk, lean meat, and vegetables. Although Goldberger could not yet identify the pellagra preventive, he knew what kind of foods contained it and what the dire results were when they were absent. Like beriberi and scurvy, pellagra was the result of a nutritional deficiency and not an errant microbe. All the 11 men at the end of the experiment were pale, weak, and emaciated. All were pardoned and released.

The final piece of the pellagra puzzle was set in place by researchers at the University of Wisconsin and announced modestly 22 years later and 8 years after Goldberger had died. Dr. Conrad A. Elvehjem and his colleagues reported their breakthrough in a letter to the editor of the September 1937 issue of the *Journal of the American Chemical Society*. Elvehjem stated that they had found it "most interesting" that "black tongue" was caused by a deficiency of nicotinic acid (niacin). Physicians by now were curing pellagra with liver extract. They learned that rats on a diet deficient in the "P-P factor," as Goldberger had understood it, were stimulated to grow with nicotinamide and nicotinic acid, both substances synthesized from liver extract. Because there was no rodent equivalent of pellagra, the scientists began working with dogs. After inducing black-tongue disease using a diet developed by Goldberger—yellow corn, casing, cottonseed oil, and mineral supplements—Elvehjem and Koehn in the Department of Agricultural Chemistry at the University of Wisconsin confirmed that nicotinic acid affected the canines dramatically. Dogs that got a single dose were hungry and with their improved appetite grew and the black-tongue lesions disappeared.

In 1938, Tom Spies, at the University of Cincinnati, College of Medicine, started giving humans small doses of nicotinic acid, none of whom had pellagra. They developed flushing and tingling of the skin but no serious side effects when the drug was given intravenously. After establishing that healthy subjects and a few nonpellagrins tolerated nicotinic acid well, Spies gave a selected group of pellagrins both oral and injections of nicotinic acid but not the Goldberger diet. Evidences of pellagra improved, confirming that nicotinic acid was the deficient product. Another study at the University of Wisconsin demonstrated that corn consumption depressed the level of nicotinic acid in the body. White corn, the kind favored in the South, was even more deleterious that yellow corn. Later, it was learned that tryptophan could be converted into nicotinic acid under certain conditions. Thus, pellagra was a deficiency of both tryptophan and nicotinic acid. Other B-vitamins, pyridoxine, and riboflavin, are involved in the metabolism of tryptophan and pyridoxine is required to synthesize niacin from tryptophan. Biochemistry was such a new field that Goldberger lacked the tools to analyze fully the ramifications of his research observations.

In the early 1960s, it was demonstrated that niacin was a good cholesterol-altering drug and indeed it was the first cholesterol lowering drug. Thus, the deficiency which produced pellagra, which was cured by an atherogenic diet, namely milk, meat, butter, and eggs resulted in elevating the blood cholesterol values leading to an increase in the frequency of atherosclerotic events. Niacin preceded both the acid resins and the statins as cholesterol-altering agents. A full circle so to speak.

Disclosures

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