The History of Pellagra, Its Recognition as a Disorder of Nutrition and Its Conquest

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THE ANCIENTS have left no leads regarding the existence of pellagra. Hippocrates, Galen, and Avicenna writing at widely separate times described no disease resembling it. Whether the condition existed among the Mexican or North American Indians is not known, though it is most likely that the early explorers would have described it. Since it is a man-made disease caused by a rather specific type of poor diet, it seems unlikely that it emerged in Spain as an epidemic about 1730 without having been present sporadically for some years. In fact it already had the popular name, *mal de rosa* when Casal first described it in 1735.

The following is a brief synopsis of the history of pellagra, omitting reference to hundreds of important contributions toward its conquest.

What does seem certain is that pellagra followed closely upon the extensive use of Indian corn for food, and this relation was noted by Casal. It was recognized in Italy in 1740 and Frapolli in 1771 attributed it to the extensive consumption of maize as "polenta," plus exposure to the sun. By 1818 it was widely prevalent in the southeastern provinces of France, and in 1830 was reported from Roumania where it had been known to exist for 16 or 18 years. It was found in Austria in 1887 and in Hungary during the following year. Egypt and Russia recognized it in the early 1890's. Here in the home of maize we do not know when pellagra appeared. Grey in Utica, New York, and Tyler in Summerville, Mass., each reported a case in 1864. The disease was diagnosed in retrospect among the Union prisoners at Andersonville but any confirmation is lacking. H. F. Harris of Atlanta in 1902 described what he considered the first authentic instance in this country. Babcock, however, reviewing the records of the South Carolina State Asylum believed that there was convincing evidence that the disease had been endemic among the inmates since 1828. Casal had emphasized the dementia of pellagra, in this country it was soon to fill the asylums of the southern states.

However high the threshold of suspicion of the American medical profession, it seems unlikely that pellagra was endemic before 1900. In 1906, Searcy reported an epidemic among the inmates of the Alabama State Asylum for Negroes, and during the ensuing year it became evident that the disease was already a major health problem throughout the Southeast. The specific reason for the explosive nature of the outbreak will never be known, though several contributing factors were probably significant. Cotton was ruinously cheap and wages correspondingly low while food prices were very high. Very few animals for food were raised, and Western meat was beyond the means of the tenant farmer and the mill worker. More important perhaps was a change in the character of the corn meal during the preceding decade. Before 1900 the bulk of the meal used in smaller towns and practically all that consumed in rural areas was locally ground in grist mills which more often than not were water-driven. "Water-ground" meal was coarsely bolted or not at all and retained much of the germ and hull of

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the grain. About the turn of the century, finely bolted meal produced by large milling companies made its appearance. This so-called Western meal was thoroughly degerminated to prevent the development of rancidity during storage and shipment. The meal looked better, kept better, and made more palatable bread. Also, it was much simpler for the countryman to go to the store or commissary and buy a sack of meal than to haul corn to the grist mill and return in a day or two for the ground product. In the towns, the keeping qualities of Western meal appealed to the grocers, so they stocked it exclusively. Thus, in a few years the staple cereal food of millions of people changed from what was essentially a whole grain to a rather highly refined carbohydrate that carried little to facilitate its utilization.

At the time, the general reaction of the populace including the medical profession was dismay and frustration. In the contemporary state of knowledge such an epidemic of disabling and often fatal disease could be due only to some unknown infection or subtile toxin. During the years which followed, an enormous amount of investigation was directed toward proving one or the other of those theories. Searcy's emphasis upon the mustiness of the meal used at the Alabama asylum and its heavy infection with bacteria and fungi furnished arguments for both schools of thought. Both alike overlooked the significance of the way in which the epidemic was checked. For the "poisonous" cornbread and grits Searcy substituted wheat bread and potatoes, and his patients rather promptly recovered. For the next decade old Spanish and Italian theories of the etiology of pellagra were rediscovered and had their partisans.

To compound the prevailing confusion, pellagra was recognized in the Cook County Hospital in 1909 and in the same year was found to be endemic in the Peoria State Hospital. The people of Illinois were deeply shaken, and shortly a distinguished Commission was appointed to study the disease. The report of the Commission was dogmatic: pellagra was due to some living micro-organism. In 1912, a National Pellagra Conference was held in Columbia, South Carolina. A number of outstanding foreign pellagrologists in attendance were almost unanimous in their support of the maize toxin or "mouldy meal" hypothesis. An exception was Sambon who reiterated with vigor his conviction that the disease was due to a protozoan, yet unidentified but transmitted by the bite of the buffalo gnat. This idea appealed to many American physicians and set off new investigations wherever this pest abounded.

By now pellagra had become a matter of grave national concern, it was variously estimated that the victims might number twenty-five, fifty, even a hundred thousand with deaths upward of ten thousand per year. The United States Public Health Service assigned Goldberger to an investigation of the etiology of the disease, and the Thompson-McFadden Commission undertook the same task. The Commission worked from 1912 to 1916, employing the best available methods. Extensive epidemiologic and bacteriologic studies were made and much attention was paid to sanitation. Monkeys and baboons were injected with blood, urine, cerebrospinal fluid and tissue filtrates from patients with pellagra and were fed feces and epidermal squames with entirely negative results. The Commission's report stated emphatically that infection had not been demonstrated, that no insect vector had been found, and no relation between maize and the disease had been noted. Much stress was laid on the poor sanitation of the communities investigated and the frequency of pellagra in contacts of persons with the disease. It was noted that in general the diet of the people was poor in animal protein.

Casimir Funk in 1912 suggested that pellagra might be a deficiency disease due to the lack of a "vitamine" in maize and Osborne and Mendel in 1914 demonstrated that cystine and tryptophan are essential for nutrition and growth of animals and called attention to the scarcity of those amino-acids in zein. These observations were well known to Goldberger, and he seems to have kept them in mind throughout the years, but for him it was necessary first to prove the dietary origin. During the first two years of his research, he made extensive epidemiologic studies of communities

and institutions where the disease was rife and was more than ever convinced that diet held the answer to the problem.

In a Mississippi orphanage and in the Georgia State Hospital in Milledgeville, he was able to cure the disease and prevent recurrences by adding liberal amounts of milk and eggs to the institutional diet. The next objective was to produce pellagra in previously healthy individuals by feeding them a diet similar to that of the Mississippi orphanage. The opportunity came in 1915 when a group of convicts at the Rankin Farm of the Mississippi State Penitentiary volunteered to undergo the experiment in return for pardons upon its completion. Twelve men made up the squad, and after a six-week period of observation to establish a base-line, the test was started on April 15, 1915. The diet consisted of corn meal, grits, cornstarch, wheat flour, rice, cane syrup, sugar, sweet potatoes, small amounts of turnip greens, cabbage and collards, and a liberal portion of pork fat. The average daily intake per man was protein, 41–54 g, fat, 91–134 g, carbohydrate, 387–513 g; the protein was from 80 to 97 per cent of cereal origin. One convict left the squad, but six of the remaining volunteers had developed the disease by October 31 when the experiment was terminated. In the conclusion of his report, Goldberger stated, "Pellagra may be prevented completely by a suitable diet without intervention of any other factor, hygienic or sanitary. There is no sound evidence that the disease is controllable in any other way." He also wrote, "In relation to the production of pellagra, this study suggests that the dietary factors to be considered as possibly essential are (1) an amino acid deficiency; (2) a deficient or faulty constitution of the mineral supply; possibly, but doubtfully, (3) a deficiency in the fat soluble vitamine intake; and perhaps (4) an as yet unknown (vitamine?) factor."

By this time the infectionists had rallied their forces, and there was much question whether the negative animal inoculation experiments of the Thompson-McFadden Commission could be applied to man. Goldberger and 15 courageous colleagues accepted the challenge and undertook the crucial experiment. At Spartanburg they injected themselves with blood, swabbed their throats with nasopharyngeal secretions and swallowed the excreta and squames from patients severely ill with pellagra. (Later in the experiment they put the feces, urine, and squames in capsules.) Some of the volunteers felt a bit qualmish after the dosing, but after six months no person had become ill.

During the ensuing years Goldberger sought the elusive substance lacking in a pellagra-producing diet. With Tanner he tried the addition of foods rich in all the vitamins known at that time, and failing to prevent recurrences, concluded that the deficiency was not of a vitamin but of amino acids. He reported improvement in two pellagrins whose diet was supplemented with cystine and one who received cystine and tryptophan; this was in 1922. The same year, with Wheeler, he was able to produce blacktongue in dogs with a diet essentially the same as that used in the Rankin Farm experiment and later to cure it by the addition of meat, milk, or yeast. This observation was soon applied to human pellagra at Milledgeville, and yeast produced dramatic improvement in all patients who were able to swallow and retain the 50 to 100 g per day which were required for cure.

It was now 1924 and during the nine years since the Rankin Farm experiment, the disease had maintained a steady increase throughout the South. Thanks to Goldberger's propaganda and the influence of Italian pellagrologists, dietary treatment had been almost universally adopted in hospitals so that mortality rates were lower but total deaths were not materially affected. Prevention by diet was never practical because of economic conditions as well as stubborn food habits.

Further investigation of yeast showed that the factor curative and preventive of blacktongue and pellagra resisted degrees of moist heat that entirely destroyed the beri-beri preventive factor. It was also found that the substance, now called "pellagra preventive factor" by Goldberger could be adsorbed on fuller's earth and eluted therefrom, and that the eluates were active in the cure and prevention of the disease. This led Goldberger to revert to the vitamin deficiency theory which he

had suggested some years before. Had facilities been available, the problem might have been solved at that time, since Funk had already identified nicotinic acid in yeast extracts but discarded it as a vitamin since it had no effect on beri-beri.

Voegtlin in 1914 had tried the effect of a crude liver extract with some success but abandoned the investigation when he refined the extract and found it impotent. Years later Goldberger, Wheeler, Lillie, and Rogers found dried pig's liver effective in the prevention of blacktongue. Goldberger and Rogers in 1924 tried the oral liver extract of Minot with success in the prevention of blacktongue, though Sebrell completed the experiment after Goldberger's death in 1929 and accomplished rapid cure of blacktongue with this preparation. In this year 1929 also, the incidence of pellagra reached its all time high.

On the clinical side not too much had been accomplished during the twenty-three years since the disease had been recognized. Up to 1924, hospitalized patients were fed high-protein diets, often administered by gavage and treated with a great variety of drugs of which sodium cacodylate was most commonly employed. The average mortality was 33 per cent during this era, this figure reflects the extreme delapidation of patients considered ill enough to warrant hospitalization. Complete anorexia, intractable nausea, and psychotic delusions made it impossible to administer the diet adequately. Many patients would promptly vomit after gavage, others would induce vomiting to relieve the burning pain caused by food. Dehydration and, in retrospect, electrolyte imbalance, were the rule but at that time their importance was not generally recognized. Yeast and liver extracts for oral administration reduced the mortality rate to 25 per cent but the same difficulties that beset dietary treatment were still encountered. Injectable extracts of liver for intramuscular use proved not to be potent in the amounts used, and no crude preparation for intravenous administration had been developed. The ambulatory pellagrin seen in outpatient departments fared much better. It seldom was possible to improve the diet for any long period but those who came for help would take the yeast we gave them. Liver extracts remained too expensive to dispense to outpatients.

After Goldberger's death, Wheeler and then Sebrell headed up the research aided by many others. Up to that time the team of the U. S. Public Health Service had conducted the great bulk of the planned investigation. During the early 1930's a number of independent clinical research projects were set up throughout the country. Looking back after 30 years, one wonders how much they contributed to the actual solution of the problem but the efforts were laudable. Reported deaths exceeded 7,000 in 1928, 1929, and 1930 and there were probably more than 200,000 pellagrins in this country. The disease had truly become everybody's business.

By that time, the vitamin theory was generally accepted and whether one called the unknown vitamin "P-P factor," "vitamin G," "vitamin B_2," or just "the anti-pellagra vitamin" was unimportant. There were some even then who suspected that there might be more than one factor involved, others advanced the hypothesis of a conditioned deficiency. Riboflavin was found to be a vitamin in 1933 and pyridoxine was found to be a component of the "B group" a year later. On the basis of animal experiments in which various species of animals were used by different observers, both of these new members of the vitamin B complex were thought for a time to be the antipellagra vitamin. Much time was to pass before their true role was recognized.

Working separately, Elvehjem and his group, and Lepkovsky and Jukes with their colleagues, had found that liver extract and rice-bran extract contained a substance which was distinct from the anti-beri-beri factor of Funk (now called vitamin B_1); vitamin B_6, and riboflavin. This substance was generally known as "the filtrate factor." In 1936 Fouts, Lepkovsky, Helmer, and Jukes reported two cases of pellagra which responded to treatment with a liver preparation containing "filtrate factor" but free of vitamins B_1, B_6, and riboflavin. During the same year Sebrell, Onstott, and Hunt treated blacktongue in dogs with filtrate factor from rice bran and obtained ex-

cellent results, but in from 54 to 117 days after treatment was started, dogs developed collapse and stupor and died rapidly. Sebrell's group recognized the symptoms of "yellow liver" which they had previously described, a condition produced by certain of their deficient diets. They also noted that rats on a diet lacking riboflavin developed a similar change in the liver. Following up this observation when a surviving dog from the "filtrate factor" experiment, free from symptoms of blacktongue, developed those of "yellow liver," they treated it with riboflavin injected intramuscularly and in twelve hours recovery was complete. Sebrell then recognized that the blacktongue-producing diet was deficient both in the "antipellagra vitamin" and riboflavin and that while the "filtrate factor" contained something which cured the gastrointestinal and cutaneous manifestations of blacktongue, riboflavin deficiency developed during its administration. He also made the prophetic suggestion that it might be dangerous to treat patients with highly purified preparations of the pellagra-preventive factor, since the absence of unrecognized dietary essentials in such materials might lead to the production of illness other than pellagra.

It seems unnecessary to state, in this company, that the case was broken by Elvehjem, Madden, Strong, and Wooley early in 1937 when they identified the anti-blacktongue factor in liver extract as nicotinic acid. Their discovery was applied immediately to human pellagra wherever the disease was being studied. The results were truly dramatic. No longer did patients die because they could not retain food, yeast, or liver extracts. Nicotinic acid amide or sodium nicotinate could be given intravenously with lifesaving effect.

During the first year of nicotinic acid therapy it was noted that several patients, whose glossitis, dermatitis, diarrhea, and dementia were cured, retained certain lesions, or acquired them while being maintained on the basal pellagra-producing diet supplemented with nitocinic acid. Seborrheic dermatitis of the face, dyssebacia over the malar eminences, nose or chin, fissures of the commissures of the lips and eyelids persisted in some patients and developed in others. The tongue after the healing of the pellagrous glossitis, acquired a striking purplish-red or magenta color and the newly regenerated filiform papillae became flattened or mushroom shaped; concurrently there was scaling of the lips and redness of their buccal surfaces. Often there was complaint of burning and hyperaesthesia of the lips, tongue, and pharynx. These phenomena were at the time thought to be evidence of relapse, but in December 1938, Sebrell and Butler reported the experimental production of such lesions by a diet deficient in riboflavin with cure following administration of that vitamin. Thus Sebrell's suggestion that blacktongue and perhaps pellagra might be manifestations of deficiency of more than one essential dietary factor was justified.

While conducting further investigation of the riboflavin deficiency components of the pellagra syndrome we in Augusta became interested in superficial corneal vascularization which had been noted in riboflavin-deficient rats by Bessey and Wolbach. In this work we were privileged in having the collaboration of Sebrell and Butler and of Kruse. Our findings indicated that this lesion, though not specific, is probably the earliest sign of human ariboflavinosis.

With nicotinic acid available and quite cheap, it may seem strange that the elimination of endemic pellagra required about five years more. Yeast had been plentiful and cheap; it was furnished free by the American Red Cross and by state and county health agencies, yet the disease increased during the yeast era because the problem of prevention could not be solved. Ignorance and inertia on the part of that segment of the population which produced the pellagrins were not the whole answer. Poor food habits, economic stress, and the enormous backlog of chronic malnutrition were more important. In 1940 there were still more than 2000 reported deaths in spite of all the effort, educational and therapeutic, put forth by federal and state health organizations, the Red Cross and local welfare.

The second world war, however costly in lives and treasure, may be thanked for the conquest of pellagra in this country. The great

increase in employment and the mobilization of the armed forces provided almost everyone with an income, either from a job or a soldier's pay. The enrichment of flour put a reasonable quantity of B-vitamins back into the diet. Rationing inspired even the most backward souls to buy and eat the good high-protein foods to which they had never before aspired. Since 1945 pellagra has been a clinical curiosity seen only in the occasional food-faddist, senile recluse or chronic alcoholic. In fact, it requires considerable ingenuity at the present time to develop the disease, what with the flour and meal and grits and rice all expensively enriched with the things the mills have carefully removed.

Though pellagra ceased to be a clinical problem, the biochemical puzzle of the exact relation of diet to the disease remained unsolved. It had been observed many times that there was no direct relationship between the nicotinic-acid content of diets and their efficacy in producing blacktongue or pellagra. This suggested that there might be some other substance which could substitute for or be a precursor of nicotinic acid. The possibility of the existence of an anti-vitamin in corn was considered also. Krehl, Tepley, and Elvehjem in 1945 found that rats can synthesize niacin from tryptophan and that tryptophan supplements minimal amounts of nicotinic acid in the diet. They also showed that corn causes a marked increase in the nicotinic acid requirement. Other observers demonstrated that the same niacin-tryptophan relation exists in mice, dogs, and swine. The derivation of the vitamin from tryptophan was first reported in man by Vilter in 1949 and confirmed by Goldsmith and by Singal. More recently it has been proved that both riboflavin and pyridoxine are required for the metabolism of tryptophan and that pyridoxine is essential for the synthesis of niacin from the amino-acid.

While pellagra can develop without maize entering the picture, its prevalence in a maize-eating population can now be clarified. A diet low in good protein and containing large amounts of corn actually increases the requirement for nicotinic acid, at the same time blocking its endogenous production. If there is deficiency of riboflavin and pyridoxine as well, the utilization of what little tryptophan may be available is impossible and the diet is rendered virtually niacin-free.

At the end of the story, it is evident that many have been correct in their ideas of the genesis of the scourge. Casal, Frapolli, and the old Italian zeists were right. Funk's surmise of a vitamin deficiency and Osborne and Mendel's suggestion of amino-acid deficiency were right. Goldberger was right on three counts, diet, a vitamin, and an amino acid. Sebrell, Onstott, and Hunt were right when they suspected a multiple vitamin deficiency and Elvehjem and his group and Singal were right in pursuing the elusive tryptophan-niacin relationship.