Epidemiology in History

The Thompson-McFadden Commission and Joseph Goldberger: Contrasting 2 Historical Investigations of Pellagra in Cotton Mill Villages in South Carolina

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As pellagra reached epidemic proportions in the United States in the early 20th century, 2 teams of investigators assessed its incidence in cotton mill villages in South Carolina. The first, the Thompson-McFadden Commission, concluded that pellagra was likely infectious. The second, a Public Health Service investigation led by Joseph Goldberger, concluded that pellagra was caused by a dietary deficiency. In this paper, we recount the history of the 2 investigations and consider how the differences between the 2 studies’ designs, measurements, analyses, and interpretations led to different conclusions. Because the novel dietary assessment strategy was a key feature of the Public Health Service’s study design, we incorporated simulated measurement error in a reanalysis of the Public Health Service’s data to assess whether this specific difference affected the divergent conclusions.

epidemiology in history; measurement; multilevel epidemiology; nutrition

Pellagra

Pellagra, meaning “sour skin” in Italian, manifests through the “4 Ds”: dermatitis, diarrhea, dementia, and death. It was first formally described among Spanish agricultural workers in 1735 but remained rare in America until the early 20th century (1). Then, in the period from 1906 to 1940, it reached epidemic proportions, resulting in more than 3 million cases and 100,000 deaths (2). Cases were most predominant among the socially disadvantaged: almost always among the very poor and disproportionately among blacks and women (3, 4).

As of the early 20th century, pellagra’s etiology was unknown, allowing some to believe it had an infectious origin (5). Others believed pellagra was caused by poor diet, either following Casimir Funk’s emerging theory of vitamin deficiency (6) or the longstanding belief that spoiled corn contained a toxic agent (7, 8). Both the infectious and dietary deficiency hypotheses were supported by recent discoveries. In the period following Robert Koch’s identification of Bacillus anthracis in 1875, many diseases of unproven etiology, including tuberculosis, cholera, pneumonia, scarlet fever, and diphtheria, had been linked to bacteria. Given the resemblance pellagra bore to tuberculosis (e.g., endemic in environments marked by poverty and poor sanitation and amenable to treatment with environmental change, yet prone to relapse after active treatment ended (9)), it was reasonable to expect to find another infectious cause of pellagra. Meanwhile, Christiaan Eijkman’s finding that thiamine deficiency was the sole cause of beriberi disease provided a model for disease caused exclusively by nutrient deficiency, even in a diet with adequate caloric content (10).

With etiology uncertain, early investigations in the United States described the pellagra epidemic patterns. Throughout Appalachia, pellagra was prevalent in villages where residents were mainly employed by a cotton mill (11), and it was associated with seasons, poverty, poor sanitation, and, potentially, diet (12). The growing epidemic led leaders in the affected states to pressure for more intensive investigations.

The Thompson-McFadden Commission

Through the influence of George Miller, president of the New York Post-Graduate Medical School, mining magnate Robert M. Thompson and cotton merchant Henry McFadden together donated funds for a commission bearing their names to investigate pellagra. The Thompson-McFadden Commission, led by Joseph F. Siler and Philip E. Garrison, 2 officers in the Armed Services Medical Corps, and Ward J. MacNeal, a doctor affiliated with New York Post-Graduate Medical School, investigated the epidemic on a large scale.
The investigation, which lasted from 1912 to 1914, focused on the Spartanburg, South Carolina, area because of local cooperation, personal interest of South Carolina Senator Ben Tillman, and pellagra’s prevalence in the area (4, 13). An initial survey of individuals with pellagra described the local epidemic conditions (14, 15). Afterward, the Commission chose 6 cotton mill villages (Inman Mills, Whitney, Pacolet Mills, Saxon Mills, Arkwright, and Spartan Mills) to explore both dietary and infectious hypotheses (16). Every household in these villages was canvassed, with an interviewer asking 1 household resident (“usually the housewife” (16, p. 294)) for the individual age, sex, occupation, residential history, and pellagra status of each resident, as well as questions about the consumption of corn meal, grits, wheat flour, fresh meat, cured meat, lard, canned foods, milk, eggs, and butter. A resident was considered to be a case if a skin lesion was never, for a total of 7 categories (Table 1). Food consumption was categorized as year-round or seasonal, and as daily, habitual (less than daily but at least twice a week, on average), rare (twice a week or less), or rarely.

The investigation analyzed individual- and household-level diets as causes of pellagra, dismissing a dietary cause (Table 2). Most foods, including meat and corn, were found to have no association with pellagra. An observed negative association between milk consumption and pellagra was noted but dismissed because milk’s “use did not fully insure against the development of the disease” (16, p. 373). Two findings appeared to contradict a dietary hypothesis. First, in contrast to beriberi, pellagra was almost never found among nursing infants (17). Second, within the surveyed villages, pellagra was more common among whites than blacks, in spite of blacks’ perceived worse diet (17).

The infectious hypothesis was explored using an ad hoc classification of every house in the villages as being located, as of 1912, in zone 1 (containing a pellagra case), zone 2 (adjacent to a house with a pellagra case), or zone 3 (not adjacent to a house with a pellagra case). Individual zone assignment of residents who had lived in the zone for at least 2 weeks provided zone-specific incidence rates among all villages, yielding a striking inverse gradient with distance from pellagra cases consistent across villages (Figure 1). The lower incidence of pellagra in villages with better sanitation systems was also consistent with the infectious hypothesis (17), and the Thompson-McFadden Commission ultimately concluded that an infectious etiology was more likely than a dietary one.

Goldberger and the Public Health Service investigation

As the Thompson-McFadden Commission’s work concluded, the pellagra epidemic continued, and the U.S. Congress appropriated funding for a major investigation. In 1914, Joseph Goldberger, who had distinguished himself in the Public Health Service by combating yellow fever, dengue fever, typhoid fever, measles, and typhus, was appointed to lead the investigation. Goldberger reviewed the literature and concluded that pellagra had a dietary origin because 1) outbreaks occurring in institutional settings never affected the staff of the institutions (18); 2) among poor Southern whites, outbreaks and diet followed a similar seasonal pattern.

Table 1. Food Consumption Categories in the Thompson-McFadden Commission’s Household Canvass, South Carolina, 1912–1913

<table>
<thead>
<tr>
<th>Period of Consumption</th>
<th>Food Consumption Category</th>
<th>7 Times/week</th>
<th>2–6 Times/week</th>
<th>Fewer Than 2 Times/week</th>
<th>0 Times/week</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seasonal</td>
<td>Part-time daily</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Part-time habitually</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Part-time rarely</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Never</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Year-round</td>
<td>Daily</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Habitually</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Rarely</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 2. Selected Results From the Thompson-McFadden Commission’s Investigation of Pellagra Incidence in Cotton Mill Village Households in Relation to Self-Reported Consumption of Certain Foods, South Carolina, 1912–1913

<table>
<thead>
<tr>
<th>Timing and Frequency of Consumption</th>
<th>Total No. of Households</th>
<th>Households With Incident Case</th>
<th>Total No. of Households</th>
<th>Households With Incident Case</th>
<th>Total No. of Households</th>
<th>Households With Incident Case</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. %</td>
<td>No. %</td>
<td>No. %</td>
<td>No. %</td>
<td>No. %</td>
<td>No. %</td>
</tr>
<tr>
<td>Year-round</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Daily</td>
<td>414</td>
<td>38 9.1</td>
<td>13</td>
<td>2 15.3</td>
<td>527</td>
<td>36 6.8</td>
</tr>
<tr>
<td>Habitually</td>
<td>161</td>
<td>17 10.6</td>
<td>151</td>
<td>21 13.3</td>
<td>112</td>
<td>9 8</td>
</tr>
<tr>
<td>Rarely</td>
<td>85</td>
<td>9 10.6</td>
<td>337</td>
<td>33 9.7</td>
<td>121</td>
<td>9 7.4</td>
</tr>
<tr>
<td>Seasonal</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Daily</td>
<td>69</td>
<td>6 8.7</td>
<td>8</td>
<td>1 12.5</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Habitually</td>
<td>25</td>
<td>2 8</td>
<td>261</td>
<td>23 8.7</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Rarely</td>
<td>11</td>
<td>4 36.4</td>
<td>45</td>
<td>4 8.9</td>
<td>1</td>
<td>1 100</td>
</tr>
<tr>
<td>Never</td>
<td>100</td>
<td>9 9</td>
<td>46</td>
<td>1 2.1</td>
<td>117</td>
<td>24 20.5</td>
</tr>
</tbody>
</table>
Although pellagra was associated with poverty, it rarely affected poor farmers with cattle (1, 19); and 4) pellagra’s association with diet even among individuals with a calorically adequate but monotonous diet bore similarities to beriberi and scurvy (20). Goldberger’s prior failure to transmit pellagra in monkeys may have given him a perspective the Thompson-McFadden Commission lacked (21).

Working from the vitamin deficiency hypothesis, Goldberger used broad dietary changes to prevent pellagra in an orphanage and to cause and subsequently cure pellagra in a prison (22, 23). He next worked to rule out the infectious hypothesis by experimentally using nasal secretions, scabs, blood, urine, and feces from pellagrins (i.e., individuals with pellagra) to attempt to transmit pellagra to willing subjects (including himself, his wife, and his close associates) using techniques (e.g., ingestion, intramuscular injection, subcutaneous injection) that propagated other diseases; none of these attempts was successful (24). Yet despite this evidence in favor of a solely dietary hypothesis, Goldberger’s views were criticized, including by members of the Thompson-McFadden Commission, who argued that the selected populations were different than those most at risk (25), and the diet that Goldberger believed had induced pellagra in prisoners had in fact merely weakened the body’s resistance to an as yet unidentified infectious agent (1).

Therefore, Goldberger, with the support of the Public Health Service, undertook to show that pellagra in the general population could also be explained by diet. He followed up on the Thompson-McFadden Commission’s study of pellagra in cotton mill villages by undertaking another study in an overlapping set of cotton mill villages. The Public Health Service gathered data at the individual, household, and village levels using a household-by-household canvass and assessed both the dietary and the sanitation-mediated infectious hypotheses in a study closely resembling the Thompson-McFadden Commission’s, yet with 2 notable differences.

The first difference between the 2 studies was the extraordinary attention given by the Public Health Service to diet and pellagra assessment, including an integration of administrative and interview data that, to our knowledge, was unique for its time. Cohort studies preceding these pellagra investigations were based either on vital statistics alone (e.g., the work by Weinberg (26)) or on medical record abstraction (e.g., the work by Lane-Claypon (27)). The case definition required clearly defined, bilaterally symmetrical dermatitis as assessed by Goldberger or Goldberger’s assistant, G.A. Wheeler, who was also a physician. (Figure 2) (28). A 15-day household diet just prior to the peak pellagra season (between April 16 and June 15) was derived from food supply assessed through company store records and supplemented by housewife surveys of the quantity and value of food items obtained from other sources (e.g., produced at home, given to the household, or purchased from neighbors, farmers, or hucksters). Individual food supply was then weighted using the Atwater scale (for more detail, see Web Appendix 1 available at http://aje.oxfordjournals.org/).

The second major difference was the Public Health Service’s selection of a slightly different set of cotton mill villages, Spartan Mills and Pacolet Mills, the larger villages in the Thompson-McFadden study, were replaced with Newry, Seneca, and Republic. The change in villages was likely related to a desire to compare sanitation levels in relation to pellagra incidence between villages. The Thompson-McFadden Commission had previously invoked poor sanitation as supporting an infectious hypothesis by contrasting Seneca’s

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pellagra incidence with Newry’s in an analysis focused on sanitation alone (29). Republic, like Newry, was unusual among cotton mill villages in having an improved sewage system.

The Public Health Service study confirmed several previous results. The peak season for pellagra was late spring (12). Pellagra was positively associated with young age (between 2 and 10 years) regardless of sex and with female sex in adulthood (13, 30). Pellagra was much more common among poor households (12) and was associated with diet (Table 3). At the village level, pellagra was highly variable (Figure 3), but that variability was not associated with sanitation (which varied between villages but did not covary with pellagra incidence) (31, 32) or with poverty (which was roughly comparable in all villages) (33).

These findings did not conclusively implicate diet as the cause of pellagra. No single food or food category was present in all nonpellagrous households and missing in all pellagrous households. Furthermore, because poverty was a cause both of poor diet and of squalid conditions permitting infectious agents to proliferate, a dietary association with pellagra did not fully distinguish between dietary and infectious etiological hypotheses (Web Figure 1). To disentangle the effects of poverty and poor diet, Goldberger supplemented his between-household comparison with a between-village comparison in an early form of multilevel epidemiologic analysis. Having previously shown that sanitary conditions at the village level were unrelated to pellagra incidence, and that income distribution, food prices, and individuals of susceptible ages were comparable between villages, Goldberger compared a village with high incidence of pellagra, Inman Mills, to one with a single case, Newry. What differed between the 2, he argued, was food supply. Inman Mills had a company store with little fresh food and almost no nearby farms, whereas Newry had a well-stocked store and a wealth of nearby farmers selling food in town. Household-level purchase records indicated far more fresh meat and milk in Newry diets, even among the very poor. Thus, community conditions of food availability provided the best explanation for the difference in pellagra incidence between Inman Mills and Newry (33). By quantifying how the availability of food within the village shaped the specific foods consumed by individuals within households, Goldberger identified dietary

Figure 2. Reproduction of a drawing from a 1913 paper on pellagra in Africa with shading to show where lesions characteristic of pellagra were found on the body (44). Ward J. MacNeal of the Thompson-McFadden Commission included this drawing in a letter to the editor of the Journal of the American Medical Association arguing that the pellagra that Joseph Goldberger and G.A. Wheeler had induced in prison inmates did not follow the characteristic lesion pattern (45). This criticism may have led to the case definition in Goldberger and Wheeler’s subsequent investigation of pellagra in cotton mill villages in South Carolina. Reprinted from Trans Royal Soc Trop Med Hyg. 7(1):32–56. Copyright ©1913 Oxford University Press. All rights reserved.
not fully explained until biochemical analysis techniques included a transition from primarily growing food, which was explained by diet; changes in the Southern economy (which Furthermore, the recent emergence of pellagra could also be sizes of those foods; and village determined access to food. both the ability to purchase high-quality food and portion to supplement diet outside the home; income determined and sex were related to status at the dinner table and ability deficiency patterns, the mechanisms of which that were not fully explained until biochemical analysis techniques developed. From these findings and analogy with beriberi, Goldberger wove a narrative highlighting the role of diet in explaining pellagra variation through multiple levels of analysis: age and sex were related to status at the dinner table and ability to supplement diet outside the home; income determined both the ability to purchase high-quality food and portion sizes of those foods; and village determined access to food. Furthermore, the recent emergence of pellagra could also be explained by diet; changes in the Southern economy (which included a transition from primarily growing food, which was then available in local markets, to producing cotton) had led to large-scale dietary changes (34). Overall, this narrative, coupled with prior results of dietary experiments, made a strong case for a dietary cause of pellagra.

**Why the investigations reached different conclusions**

Goldberger’s hypothesis was ultimately found to be correct: individuals with diets deficient in niacin (vitamin B3) and tryptophan (which the body converts to niacin) develop pellagra (35). Yet the Thompson-McFadden Commission, a well-funded, well-intentioned, and professionally run study reached the wrong conclusions. Why did the Commission fail? We hypothesize that the failure was due to inaccurate dietary assessment, lack of between-village variability, and an interpretation of data shaped by an a priori assumption of infectious etiology.

First, the Thompson-McFadden Commission’s dietary canvassing strategy was not as accurate as the Public Health Service’s use of company store records. By limiting dietary assessment to a single per-household interview and not considering household composition, the Commission could not account for seasonal variation in diet or for variations in portion size among individuals and households. Furthermore, in a context of severe poverty, some respondents may have reported on idealized diets rather than their actual diets. It is possible that, given the stigma attached to pellagra (2), those with disease may have overreported eating meat for social desirability reasons, although we have no data from which to assess this hypothesis today. Additionally, the Commission’s acceptance of patient and physician reports of pellagra may have resulted in the inclusion of cases of other diseases causing dermatitis. The most likely such disease is ariboflavinosis, a disease caused by riboflavin deficiency, which also results in skin lesions. Ariboflavinosis lesions are characteristically located in the mouth and genitals rather than on the extremities, as in pellagra (36); the Public Health Service’s case definition likely would have excluded ariboflavinosis (19).

Second, the Public Health Service’s selection of villages to canvass was also superior in terms of exposure and disease variability. By including both Newry, with its broader food supply and improved sanitation system but no cases of pellagra, and Republic, with an improved sanitation system but prevalent pellagra, the Public Health Service was able both to examine a greater range of dietary conditions than the Thompson-McFadden Commission had been and to distinguish between the effects of improved diet and improved sanitation.

Finally, the Thompson-McFadden Commission ignored the evidence for the dietary hypothesis, downplaying an observed protective association with milk because some cases of pellagra reported consuming milk. There is evidence, however, that the Commission could have interpreted its own data differently. In 1914, Edward Vedder, a nutritionist, wrote a report enumerating the resemblances between beriberi and pellagra (37). Invited by the Commission to investigate their data, Vedder noted that the age and sex patterning, the seasonality of the disease, and the lack of correlation between population density and pellagra incidence supported the dietary hypothesis. Vedder also observed that residents of Newry, whose dietary patterns the Thompson-McFadden Commission had not assessed but who were known to have a superior food environment, had little to no pellagra. He further pointed out that the Commission’s dietary survey did not capture portion size, and that diet should be considered as a whole rather than by individual foods. Finally, Vedder noted 2 flaws with arguments for the infectious hypothesis. First, contact tracing was nearly meaningless in a context in

<table>
<thead>
<tr>
<th>Food Item and Adult Male Unit</th>
<th>Total No. of Households</th>
<th>Households With Incident Case</th>
</tr>
</thead>
<tbody>
<tr>
<td>Corn meal, lbs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;4.0</td>
<td>304</td>
<td>20</td>
</tr>
<tr>
<td>4.0–7.9</td>
<td>260</td>
<td>24</td>
</tr>
<tr>
<td>8.0–11.9</td>
<td>117</td>
<td>13</td>
</tr>
<tr>
<td>≥12.0</td>
<td>61</td>
<td>4</td>
</tr>
<tr>
<td>Fresh meat, lbs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;1.0</td>
<td>495</td>
<td>54</td>
</tr>
<tr>
<td>1.0–1.9</td>
<td>131</td>
<td>4</td>
</tr>
<tr>
<td>2.0–2.9</td>
<td>61</td>
<td>2</td>
</tr>
<tr>
<td>3.0–3.9</td>
<td>36</td>
<td>1</td>
</tr>
<tr>
<td>≥4.0</td>
<td>18</td>
<td>0</td>
</tr>
<tr>
<td>Fresh milk, qts</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;1.0</td>
<td>154</td>
<td>28</td>
</tr>
<tr>
<td>1.0–6.9</td>
<td>262</td>
<td>16</td>
</tr>
<tr>
<td>7.0–12.9</td>
<td>163</td>
<td>8</td>
</tr>
<tr>
<td>13.0–18.9</td>
<td>90</td>
<td>4</td>
</tr>
<tr>
<td>≥19.0</td>
<td>58</td>
<td>0</td>
</tr>
</tbody>
</table>

* The Atwater scale accounts for the effect of household size on resources available to each individual within the household. Any male over the age of 16 years is 1 adult male unit, and women and children are calculated as proportions of an adult male unit on the basis of their expected consumption.

* 1 lb = 0.454 kg.

* 1 qt = 0.946 L.
which all residents had some contact with pellagra. Second, given that hospital staff never contracted pellagra from patients after close contact, observed clustering within households was more consistent with causation due to shared diet than to shared exposure to an infectious agent (38). Unfortunately, the Thompson-McFadden Commission missed Vedder’s ideas, arguing that the dietary hypothesis would predict simultaneous development of pellagra within a household, whereas they had observed lags of months or years between incident cases (25). However, the Public Health Service was aware of Vedder’s work (19, 33); it may have been that Vedder’s critique of the Commission’s survey motivated the Public Health Service to use a dietary assessment strategy that accounted for portion size.

**METHODS**

**Data collection**

We were unable to retrieve original individual-level data from the Public Health Service study. Our search targeted the Goldberger archive at the University of North Carolina (C. Gray, University of North Carolina at Chapel Hill, personal communication, 2013), the Goldberger archive at Vanderbilt University (C. Ryland, Vanderbilt University Medical Center, personal communication, 2013), and the Public Health Service archive. We also made personal inquiries to the Pearl S. Buck family archive (the Public Health Service’s chief statistician, Edgar Sydenstricker, was the brother of Nobel laureate Pearl S. Buck), the descendants of G.A. Wheeler, and the Milbank Memorial Fund, where junior statistician Dorothy Wiehl, who likely compiled results into the final published tables, later worked.

We therefore restricted our reanalysis to summary data extracted from papers authored by the Thompson-McFadden Commission. Our hypothesis was that inaccurate case definition and dietary assessment were 2 of the main factors preventing the Thompson-McFadden Commission from identifying the true cause of pellagra.

**Reanalysis**

The Public Health Service’s attention to assessing household diet and validating the reported cases of pellagra indicates grave concern that measurement error might blur the nature of the association between diet and pellagra (19). To understand the specific importance of measurement differences between the 2 studies, we simulated analyses the Public Health Service might have performed using methods only as accurate as those used by the Thompson-McFadden Commission. Our hypothesis was that inaccurate case definition and dietary assessment were 2 of the main factors preventing the Thompson-McFadden Commission from identifying the true cause of pellagra.
Commission and the Public Health Service investigators. We simulated measurement error in meat assessment because milk and meat were the only 2 niacin-containing foods considered by both the Public Health Service and the Thompson-McFadden Commission. Data on the relationship of fresh meat supply to pellagra were extracted from Table IX of the Public Health Service’s diet paper (19) and from Tables 49 and 50 of the Thompson-McFadden Commission’s diet paper (16). Data on village-specific pellagra incidence were extracted from Tables I and III of the Public Health Service’s sanitation paper (31) and from Tables 53, 54, 57, and 58 of Thompson-McFadden Commission’s diet paper (16).

Statistical analysis

Our analysis treated the Public Health Service data on meat supply and pellagra as the truth and simulated misclassification of both pellagra diagnosis and meat supply. Because the Commission’s canvassing strategy was as inclusive as that used by the Public Health Service (14), we assumed a sensitivity of 100% for pellagra diagnosis. However, because the Commission’s case definition allowed for patient or physician reports of skin lesions and made no mention of requiring bilateral symmetry (14), the Commission likely included some cases of ariboflavinosis in their pellagra group. Because pellagra’s yearly mortality rates among whites were relatively constant in the mid-1910s (39), we assumed that the total prevalence of pellagra in the 4 villages assessed by both investigations was equal in 1912 and 1916 and estimated specificity for the Commission’s diagnosis by assuming that the excess pellagra incidence observed by the Commission was due to ariboflavinosis misdiagnosed as pellagra. Further, because the Commission’s assessment of meat consumption was based on self-reports and was not strictly seasonal (16), we simulated misclassification of meat consumption ranging from 0% to 30% of individuals. We then compared the relation of partially misclassified meat supply to partially misclassified pellagra to assess how much weaker the trend of

Figure 4. The association between household-level pellagra incidence and A) estimate of meat supply (slope = −0.022) in the Public Health Service study, South Carolina, April 1916–June 1916 and B) in 25 data sets simulated from the Public Health Service data with pellagra measured at 98.6% specificity and with 25% of household meat supply misclassified (median slope = −0.010). Each thin line represents the slope estimate from 1 simulation; the thick line represents the median estimate. 1 lb = 0.454 kg. Public Health Service data were extracted from Table IX of the report by Goldberger et al. (19).
increasing pellagra with decreasing meat supply became. We ran 1,000 simulations at each level of meat supply misclassification. We also plotted 25 of these slopes (at 25% misclassification) to illustrate the variation in slopes in these simulations.

Both studies predate the use of modern statistics; investigators compared incidence rates visually by category to determine whether a significant relationship existed. To simulate this visual trend test in 1,000 simulations, we considered a regression line with a slope indicating an average change of 9.1 cases/1,000 subjects between categories to indicate a noteworthy relationship. We picked 9.1/1,000 as the change the Public Health Service considered “a suggestion of an inverse correlation” (19, p. 691). All analyses were performed using R for Windows, version 2.15.3 (R Foundation for Statistical Computing, Vienna, Austria). The code for simulations can be found in Web Appendix 2.

RESULTS

Application of the pellagra incidence rate observed by the Public Health Service to the Thompson-McFadden Commission data in Arkwright, Newry, Saxon Mills, and Whitney resulted in an estimated 30 excess cases of pellagra in each village. Assuming those cases were misclassified resulted in an estimated specificity of 98.6%.

Figure 4 displays the pellagra incidence rates by misclassified meat supply in the Public Health Service results and in 25 simulations, with the median slope highlighted. Simulations incorporating measurement error resulted in notably weaker associations between meat supply and pellagra. Figure 5 displays the proportion of simulations with a slope of 9.1 cases of pellagra per 1,000 subjects for each increase in meat category. At 20% of meat supply misclassified, half of the slopes were below the level the Public Health Service considered a “suggestive correlation.”

DISCUSSION

The Thompson-McFadden Commission and the Public Health Service both investigated pellagra incidence in cotton mill villages in South Carolina in the 1910s using similar survey methods, yet they came to starkly different conclusions. We believe that 3 characteristics allowed the Public Health Service to correctly determine the relation of pellagra to diet.

First, a carefully planned approach to data collection and measurement avoided misdiagnosis of ariboflavinosis as pellagra, prevented inaccuracy in dietary measurement, and accounted for variation in household composition. Our simulations showed that small amounts of exposure and disease misclassification sufficed to nullify the meat consumption–pellagra association. Although we have no evidence as to the rate of misclassification in the Thompson-McFadden Commission’s data, this may explain why the Commission found no association between pellagra and the consumption of foods we now know to contain niacin. Furthermore, this may explain why Edward Vedder, making roughly similar claims to those Goldberger made later, was not widely heeded. Second, the Public Health Service’s selection of
villages with a wider range of diet and pellagra incidence augmented the advantage of superior accuracy in data by presenting stronger between-village contrasts. Third, flexibility of analytical thought to understand that multiple levels of influence could be examined allowed the Public Health Service to identify the proper contrasts within the data. A contemporary perspective also allows us to consider the Public Health Service investigation as an early example of multilevel epidemiologic analysis (40). Diet at the individual level is notoriously difficult to assess; instead, the Public Health Service leveraged contrasts in village-level food availability and in household composition to reconcile known patterns in disease incidence with a dietary hypothesis. By comparison, the Thompson-McFadden Commission collected data at multiple levels but did not leverage the multilevel potential of the data, instead using lack of between-village variation in geographical clustering of cases as an argument for an infectious hypothesis (16). In hindsight, and using modern terminology, we can say that, for the first time that we are aware of, the Public Health Service team led by Goldberger combined 2 main features: 1) containment of misclassification using carefully collected data on exposure and outcome and 2) a multilevel analysis including individual level and several group (households and villages) levels, with the understanding that the village was what we would now term an effect modifier of the relation of poverty and pellagra (mediated by diet). Had modern statistical tools been available, the Public Health Service might have considered both the “neighborhood” (i.e., village) association with the individual-level outcome and individual-level risk factors within the same analysis. If the original Public Health Service data are ever recovered, it would be of interest to know whether modern multilevel analytical tools would provide any insight beyond the published analyses. Unfortunately, although the cotton mill village study fully convinced Goldberger of pellagra’s dietary etiology, his critics remained skeptical (1). Deciding that further epidemiologic studies would not convince them, Goldberger instead focused on finding the agent that prevented pellagra (2). Nearly 20 years after the cotton mill village studies, Elvehjem and Koehn (41) identified nicotinic acid (later renamed niacin) as the vitamin whose deficiency caused pellagra. Pellagra was fully eradicated when the niacin supplementation of flour became widespread in the early 1940s (42).

CONCLUSIONS

The Public Health Service’s dedication to collecting accurate data and its insight into the contextual shaping of risk enabled the second cotton mill village investigation to succeed where the Thompson-McFadden Commission’s did not. The Public Health Service’s investigation is an excellent example of 2 key features of effective epidemiology: careful data collection and formulation of analyses that differentiate between competing hypotheses. We believe that Goldberger deserved the Nobel Prize he might have won had he lived longer (43); his approach to studying pellagra represents a model we would do well to follow today.

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