Joseph Goldberger's research on the prevention of pellagra

Alfredo Morabia

J R Soc Med 2008 101: 566
DOI: 10.1258/jrsm.2008.08k010

Joseph Goldberger's research on the prevention of pellagra

Alfredo Morabia

Center for the Biology of Natural Systems, Queens College – City University of New York, 163–03 Horace Harding Expressway, Flushing, NY 11365, USA. E-mail: alfredo.morabia@qc.cuny.edu

DECLARATIONS

Competing interests
None declared

Funding
None

Ethical approval
Not applicable

Guarantor
AM

Contributorship
AM is the sole contributor

Acknowledgements
Additional material for this article is available from the James Lind Library website (www.jameslindlibrary.org), where it was originally published

Pellagra was first identified among Spanish peasants by Don Gaspar Casal in 1735. A loathsome skin disease, it was called 'mal de la rosa' and often mistaken for leprosy. Pellagra has sometimes been called the disease of the four Ds – dermatitis, diarrhoea, dementia and death. In 1937 it was discovered that pellagra was caused by a deficiency of the B vitamin niacin (nicotinic acid). The body's synthesis of this vitamin depends on the availability of the essential amino acid tryptophan, which is found in milk, cheese, fish, meat and eggs. Two decades before the discovery of niacin, however, epidemiological and clinical research done by Joseph Goldberger and his colleagues had identified that pellagra could be prevented by improved diet.

By 1912, the state of South Carolina alone had reported 30,000 cases of pellagra, with a case fatality rate of 40%. The disease was not confined to Southern states, however, and the US Congress asked the Surgeon General to investigate the disease. In 1914 he appointed Joseph Goldberger (1874–1929), a medical officer in the US Public Health Service, to lead the investigation.

Even though some scientists such as Theophile Roussel[1] and Casimir Funk[2] argued that pellagra was caused by something inadequate in the diet, the disease was generally thought to be due to an unidentified germ. This opinion had received strong support in 1914 by the Thompson-McFadden Pellagra Commission. This Commission, which had been set up by the US government, had conducted a house-to-house survey of pellagra cases in the cotton mill districts in South Carolina and concluded that the disease was unrelated to diet. Goldberger had a different opinion. He had observed that, in mental hospitals and orphanages, the disease affected inmates but never staff. Also, well-to-do people seemed never to develop the condition. Goldberger believed that an infectious disease was unlikely to distinguish between inmates and employees or so systematically between rich and poor, and he favoured the hypothesis that a superior diet protected people from pellagra. He had also in mind the case of beri-beri, a disease which had recently been shown to be responsive to dietary interventions.[3–5]

In 1914 Goldberger designed and implemented two experiments to assess whether improving the diet of institutionalized children and adults would prevent pellagra. The first set of institutions studied were two orphanages with a high incidence of pellagra in Jackson, Mississippi. Goldberger and his colleagues noted that the disease affected only children between 6 and 12 years of age and observed that 'after a detailed inquiry, the only explanation that could be found for the remarkable restriction of the disease to this group was a difference in the diet of the resident groups'.[6] Their diet was poor in lean meat or other animal protein food.

A parallel and analogous experiment was conducted in two women's wards (one for black patients, the other for white patients) in the Georgia State Sanitarium, the largest asylum in the South. This institution admitted a large number of patients with pellagra every year, but the objective of the study was to assess the effects of the dietary intervention in preventing recurrence of the condition, not for treatment.

The interim report

Interim results of the research were published on 22 October 1915, while the two-year experiment was still in progress.[6]

The two orphanages were referred to as 'MJ' and 'BJ'. During the summer of 1914 up to 15 September, orphanage MJ had had 79 cases and orphanage BJ 130 cases of pellagra. Although hygienic and sanitary conditions in the orphanages left much to be desired, the researchers requested that these not be modified during the experiment. Details of the diet of the residents is given in the report, but the intervention was

essentially very simple: 'at both institutions a very decided increase was made in the proportion of the fresh animal and of the leguminous protein foods': milk, buttermilk, eggs, beans and peas. The researchers restricted corn in order to reduce the proportion of carbohydrates in the diet. This was a methodological mistake, however, because it meant that the study stood little chance of debunking the hypothesis that corn actually caused pellagra, as some had claimed.

Even though all residents, pellagrins or not, received the new diet, the main outcome measured was recurrence of pellagra during the summer of 1914 among children who had already suffered from the condition. The interim results after one year of the new dietary regimen were already very encouraging: at orphanage MJ, Goldberger's team observed no recurrences among the 67 children who had reached or passed the anniversary of their previous attack, nor did they observe any new cases of pellagra among the 99 non-pellagrins who had been observed for one year. At orphanage BJ, there was one recurrence among the 105 children who had reached or passed the anniversary of their previous attack, and no incident cases among the 69 non-pellagrin residents followed for one year.

The experiment at the Georgia State Sanitarium started in 1914 (October for the black patients and December for the white patients). Potential participants had to have forms of mental illness likely to mean that they could be observed for at least a year. Nearly all eligible patients were reported to have been included – 40 pellagrins in each ward. The dietary intervention was similar to that in the orphanages, and efforts were made to ensure that no condition other than diet was changed. There were no recurrences among the 36 black and 36 white women observed through to 1 October 1915.

The final report

Although data collection for Goldberger's study had been completed by 1917, the full results were not published until 1923 as a fairly brief summary of a substantial amount of research.[7] Overall the study had involved 414 pellagrins (250 orphans and 164 asylum inmates) and 288 non-pellagrins (268 orphans and 20 asylum inmates). Of these, 126 pellagrins and 101 non-pellagrins had been followed for at least two years. There was a single recurrence in an orphan, and no incident cases.

Comment

Group comparison

Methodologically, the trial does not break new ground but it is not untypical of this phase of the evolution of epidemiological studies.[8] Goldberger and his colleagues were aware that the design of the orphanage research was not optimal, noting that 'the ideal for the experiment would have been, of course, to retain for purpose of comparison, a control group at each of the institutions. This was impracticable at the orphanages'.[6] They therefore collected data from 'other similar institutions' and found recurrence rates between 58% and 75%. Having chosen a conservative estimate of expected recurrence of 50%, they concluded that they should have observed 33 recurrences at orphanage MJ and 52 at orphanage BJ. Against this expectation, the dramatic finding of no recurrences and one recurrence, respectively, provided strong evidence of a protective effect.

Their observations in the asylum reinforced this interpretation because only two wards had been placed at the disposal of Goldberger and his colleagues. Patients in other wards who had not received the dietary intervention therefore provided 'a direct comparison'.[6] This control group had not been specifically planned. Its data are not shown in the Results section of the report but mentioned in the discussion as follows:

> 'The control group of colored female pellagrins of 1914 consists of 17 who have remained under observation for a period comparable to that of the group on the special diet. Of these 9, or 53 per cent, have already presented recurrences. The control group of white female pellagrins of 1914 consists of 15 individuals. Of these 6, or 40 per cent, have had recurrences this year. Combined, the two control groups have thus far presented an average of 47 per cent of recurrences.'[6]

Goldberger and his colleagues also analysed the asylum's records to calculate the average rate of recurrences in the years preceding the experiment. This was found to be 37.5% among white patients and even higher among black patients.

Causal inference

The approach to causal reasoning in Goldberger's papers is not structured but it prefigures today's practice, addressing as it does some elementary logical criteria for judging whether a diet poor in animal protein causes pellagra.

All the evidence indicated that the expected number of recurrences was much higher than the number observed. Thus, the *strength* of the association was the first criterion used to conclude that pellagra recurrences could 'be prevented without the intervention of any other factor than diet'.[6] The conclusion in the 1923 paper was stronger: 'The idea that pellagra is a communicable disease receives no support from this study. Pellagra may be completely prevented by diet.'[7]

Goldberger and his colleagues claimed that the dietary hypothesis had more epidemiological *plausibility* than the infectious hypothesis because pellagra recurred in the spring or early summer in 'striking *analogy*' with the occurrence of endemic scurvy and beri-beri, two diseases with a seasonal pattern which were also related to dietary deficiency. They noted, however, that the experiment did not provide a dose-response relationship, as might be observed by 'comparing the incidence of the disease in groups of families using this particular food with different degrees of frequency'. Nor could they exclude the possibility that the association was due to some potential third dietary factor other than fresh animal or leguminous protein food. One of the weaknesses of the experiment, not mentioned by Goldberger and his colleagues, was that because corn had been reduced in the experimental diet, it could not refute the popular hypothesis that spoiled maize caused pellagra.

Goldberger's critical discussion of the results of his pellagra research served him well later when he designed what will remain as his most original contribution to epidemiology – his survey of cotton mill workers in South Carolina, performed in association with Edgar Sydenstricker.[9]

In view of the importance of their discovery of how pellagra could be prevented, and their observation that 40% of the study participants in the asylum developed pellagra after reverting to the pre-trial diet at the end of the study, it is surprising that Goldberger and his colleagues took six years to report the full findings of their research, and then only in a brief report. The authors justified the delay as follows:

> 'A report covering the work and results of the first year was published in 1915.[6] It was originally intended to make a detailed presentation of the study on its completion; but the published results of the first year by White (White RG. Report on an outbreak of pellagra amongst Armenian refugees at Port Said, 1916–1917. Cairo, Egypt, 1919) among Armenian refugees in Port Said, and by Stannus (Stannus JF, Garrison PE, MacNeal WJ. J Am Med Ass 1914; 62:8–12) among inmates of Central Prison, Nyassaland, before this could be done, has rendered a detailed account [of the Mississippi experiment] superfluous. And this all the more as the later results, as will presently be seen, were in close harmony with and in complete confirmation of those of the first year.'[7]

To my knowledge, Goldberger's biographers have not commented on this six-year delay to publication. Most probably, in Goldberger's mind, it was clear by the end of the orphanages and asylum experiments that pellagra recurrences could be prevented by diet. He wanted now to show that pellagra was not transmissible between humans[10] and that the disease could be induced by a typical poor Southern cereal diet.[11]

From the standpoint of the evolution of fair tests of treatment in healthcare, the 1915–1917 pellagra experiments among orphans and psychiatric patients position Goldberger as a pioneer of dietary prevention trials. The absence of planned control group, apparently due to institutional constraints within the orphanages and the asylum, is an important weakness, but the intervention effect was so dramatic that the results could lead to strong conclusions nevertheless.

References

1 Roussel T. *Traité de la pellagre et des pseudo-pellagres.* Paris: JB Baillière et fils; 1866
2 Funk C. Prophylaxie u. Therapie der Pellagra im Lichte der Vitamin Lehre. *Muenchener mediziner Wochenschrift* 1914;**61**:698–9
3 Vorderman AG. *Onderzoek naar het verband tusschen den aard der rijstvoeding in de gevangenissen op Java en Madoera en het voorkomen van beri-beri onder de geïnterneerden.* Batavia: Jav. Boekh. & Drukkerij; 1897
4 Fletcher W. Rice and beri-beri: preliminary report on an experiment conducted in the Kuala Lumpur Insane Asylum. *Lancet* 1907;**1**:1776–9
5 Vandenbroucke JP. *The contribution of William Fletcher's 1907 report to finding a cause and cure for beriberi.* The James Lind Library; 2003
6 Goldberger J, Waring CH, Willets DG. A test of diet in the prevention of pellagra. *South Med J* 1915;**8**:1043–4
7 Goldberger J, Waring CH, Tanner WF. Pellagra prevention by diet among institutional inmates. *Public Health Rep* 1923;**38**:2361–8
8 Morabia A. Epidemiology: An epistemological perspective. In: *History of epidemiological methods and concepts.* Basel: Birkhäuser; 2004. p. 1–126
9 Goldberger J, Wheeler GA, Sydenstricker E. A study of the relation of family income and other economic factors to pellagra incidence in seven cotton-mill villages of South Carolina in 1916. *Public Health Rep* 1920;**35**:2673–14
10 Goldberger J. The transmissibility of pellagra: Experimental attempts at transmission to human subjects. *Public Health Rep* 1916;**31**:3159–73
11 Goldberger J, Wheeler GA. The experimental production of pellagra in human subjects by means of diet. *Hygienic Laboratory Bulletin* 1920;**120**:7–116