Epidemiology in History

Snippets From the Past: Is Flint, Michigan, the Birthplace of the Case-Control Study?

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In the summer of 1924, an outbreak of scarlet fever occurred in Flint, Michigan. Unable to trace it to the usual causes, particularly fresh milk, the Michigan Department of Health used a novel approach to disentangle the enigma: The 116 cases of scarlet fever were compared with 117 “controls” selected from neighbors of the quarantined cases and from patients at the City Health Center who had been treated for ailments unrelated to scarlet fever. The extraordinary culprit was ice cream, which had a frequent/occasional/none consumption prevalence of 60%, 34%, and 6% among the cases and 24%, 51%, and 25% among the controls, respectively. The 1925 report reads, “Detailed epidemiological investigation, by means of case histories and control histories on well persons, confirmed early suspicions and established the fact that the epidemic was spread by ice cream” (Am J Hyg. 1925;5(5):669–681). This forgotten epidemiologic study is the oldest study using the case-control design to have been resurrected thus far. The case-control study design may have been conceived simultaneously, but independently and for different purposes, in England (Janet Lane-Claypon’s 1926 report on the determinants of breast cancer) and the United States.

case-control studies; disease transmission; epidemiologic methods; history of medicine; ice cream; scarlet fever

The study of epidemiology’s past can resemble an archaeological dig. Much material remains unearthed. New fossils may shamble old wisdom. Consider case-control studies. The current credo links their origin to the rising interest in cancer (1, 2) and cardiovascular diseases (3–5) during the interwar period (6, 7). This interpretation, however, cannot accommodate a 1924 case-control study that was conducted in Flint, Michigan, to disentangle the causes of an intricate outbreak of scarlet fever (8). This fossil study, discovered while digging into the archives of the American Journal of Hygiene, becomes the oldest known case-control study and enriches epidemiology’s past.

In scarlet fever, group A hemolytic streptococcus typically infects the throat and produces a toxin which, when it reaches the skin after having circulated in the blood, causes the pathognomonic scarlet pigmentation. The disease can recur, and death is caused by high temperature and coma. In the United States, the incidence of scarlet fever, one of the most deadly childhood diseases in the 19th century, rapidly declined in the 20th century (9–11).

Milk has often induced epidemics of scarlet fever (12), but by 1925, the milk distributed in US cities was widely pasteurized (13). George H. Ramsey (Figure 1), then Deputy Health Commissioner for the state of Michigan, was forced to innovate methodologically when it became clear that the strange outbreak of scarlet fever that occurred in Flint during the summer of 1924 could not be traced to the consumption of milk from a specific dairy (8).

The Study

From July 22 to July 28, 1924, 41 cases of scarlet fever were reported in Flint, Michigan. The number was greater than in any other week that year and was particularly unusual for a summer month. Acting on knowledge from past experiences, investigators immediately suspected contaminated milk as being the culprit (14). While inspecting the plants and employees of milk-related industries, Howard R. Estes, Dairy and Food Inspector of the Flint Department of Health, learned that the employee of a small ice-cream manufacturer
had continued working for 3 days after the onset of a sore throat and an eruption of scarlet pigmentation. Could the milk have been contaminated after pasteurization? Ice cream was known to transmit enteric diseases such as typhoid fever. It had been incriminated in a scarlet fever outbreak in 1875, but doubts subsisted (8). In Flint, contaminated ice cream was a plausible suspect. Therefore, questions about its consumption were included in the epidemiologic and clinical histories of the quarantined cases obtained by physicians, who visited homes and swabbed the throats of all members of affected households.

By August 10, three of the 116 patients had died. Of the 83 successful cultures, 84% tested positive for hemolytic streptococci. The analysis of the cases, mostly occurring in adult men, was fruitless: No single dairy farm supplied a larger percentage of cases than would be expected based on the city’s total milk supply, and the cases had not attended a picnic, participated in a public gathering, or eaten at the same place.

The classic outbreak investigation was then supplemented by a comparative study. The published paper states, “Control histories were elicited from 117 individuals who were not attacked during the scarlet fever epidemic. Whenever practical, these histories were obtained by visiting houses in the same neighborhood in which cases were under quarantine. Other histories were procured from individuals being treated at the City Health Center for various ailments, none of them related to scarlet fever” (8, p. 670).

Cases and controls differed by gender and age but were “so much alike in other particulars that the variations [did] not destroy the value of the control series” (8, p. 673). They both “appear[ed] to be fairly representative samples of the population of Flint” (8, p. 676). There were no differences in economic status (“both the poor and the more prosperous were attacked” (8, p. 674)), sanitation of premises, histories of meals eaten away from home, and attendance at public gatherings. Lastly, frequencies of use and sources of milk supplies were also similar. Ramsey only noted that controls had had more previous attacks of scarlet fever.

The unusual culprit turned out to be ice cream, which had a frequent/occasional/none consumption prevalence of 60%, 34%, and 6% among the cases and 24%, 51%, and 25% among the controls, respectively. Figure 2 shows that the ice cream consumed by the cases predominantly came from factory A—precisely the plant where the sick production worker must have coughed or sneezed into the mix. The picture was complete after a negative Dick test confirmed the scarlet fever diagnosis of the worker and a hemolytic streptococcus of bovine origin was isolated from samples of the contaminated ice cream.

**Figure 1.** Portrait of George H. Ramsey that appeared in *The Pelham Sun* on October 27, 1939. Reproduced with the permission of Rising Media Group, LLC (Yonkers, New York).

**Figure 2.** Percentages of the total ice cream supply of Flint, Michigan, furnishing by individual ice-cream factories during the period July 21–30, 1924 (inclusive), and percentages of scarlet fever patients and controls who consumed ice cream from each of those factories during that same period. Originally Figure 3 of the paper by Ramsey (8); reproduced with the permission of Oxford University Press (New York, New York).
DISCUSSION

The protagonist of this investigation is Dr. George H. Ramsey. His “exceptional” shyness (15, pp. 122–123) did not hinder him from becoming an influential figure in epidemiology and public health. A native of Olean, New York, with a medical degree from Columbia University (1917) and a public health doctorate in epidemiology obtained in 1924 under the supervision of Wade Hampton Frost at Johns Hopkins University (15, p. 157), Dr. Ramsey split his professional life among an array of public health positions—Deputy Commissioner of the Michigan Department of Health (1921–1926), Assistant Commissioner of Preventable Diseases in the New York State Department of Health (1933–1938), Health Commissioner of Westchester County in New York (1938–1942)—and academic positions—student at Johns Hopkins in 1923 and 1924, Associate Professor of Epidemiology at Hopkins (1926–1933), and Resident Lecturer in Epidemiology at the Michigan School of Public Health (1942–1949) (15, 16). He had 2 other publications in the American Journal of Hygiene (17, 18).

The Flint study raises fascinating historical questions. Why did Ramsey choose controls? Was it because of the exceptional features of the scarlet fever outbreak or because he was an exceptionally well-trained epidemiologist?

The conditions of the Flint outbreak were ideal for contriving a new study design. The problem, slightly more complex than usual (ice cream was not an established cause of scarlet fever), defeated the classic and proven techniques of case tracking and bacteriology. Consider, for comparison, Ramsey’s investigation, the following year, of an outbreak of typhoid fever that occurred after a church dinner served in Eaton Rapids, Michigan (19). Of the 250 dinner guests, 35 contracted severe typhoid fever, and 6 died. Nearly all of the typhoid fever patients had eaten turkey, potatoes, and squash. When typhoid bacilli were isolated from both the feces and the urine of a food handler, a carrier who had prepared the squash, the problem was solved. In Flint, however, these classic techniques proved to be insufficient. Cases had not all consumed milk from the same dairy. They had not attended a luncheon, a picnic, or any type of catered mass gathering. To solve the riddle, Ramsey and the Michigan Department of Health had to supplement the failing outbreak investigation approach. They had a clue in the sick ice-cream-plant worker identified during the inspection of the local milk industry. They still had to show that the cases had eaten ice cream from that plant more often than would be expected for their source population. The idea of selecting controls to estimate this expected distribution of ice cream providers may have gushed forth as the next logical step in the investigation. The case-control comparison condemned the hypothesis that quiescent frozen streptococci, seeded in the ice cream by the sick worker, had been brought out of their torpor by the warm tongues of the cases-to-be.

Therefore, a complex problem thwarting the classic, proven methods of outbreak investigation may have spurred a methodological breakthrough. Under this simple scenario, we cannot preclude the possibility that further digs into the activities of health departments in the 1920s will reveal that case-control comparisons were commonly implemented but their findings rarely published in prominent hygiene and public health journals.

Another trait, however, sets the Flint study apart: It is an unambiguous case-control study. Participants were recruited based on the presence of scarlet fever. Controls were a combination of neighborhood and City Health Center controls. The consciousness that the two groups had to be comparable in order for the study to be valid is manifest throughout the report. Readers can judge from the tabulated characteristics of the cases and the controls. For its time, it was an exceptionally well-designed epidemiologic study. Earlier, naive, diseased-versus-nondiseased comparisons lacked directionality (20) or did not describe the characteristics of the control group (21). Notably, based on Ramsey’s study standards, the German studies of 1939 and 1943 about smoking and lung cancer are not eligible to be designated case-control studies (22, 23). More detail about the sources, recruitment, and interviews of the cases and controls would have been welcome, but there was no model to learn from. Lane-Claypon’s report on breast cancer came out only a year later in 1926 (1, 7, 24); it had 10 times more pages than Ramsey’s.

The sophistication of the Flint investigation interrogates us about the specific role of Ramsey, then one of the few well-trained epidemiologists in the United States. In 1923 and 1924, while conducting the Flint study, Ramsey was Wade Hampton Frost’s student in the Department of Epidemiology at the Johns Hopkins University School of Hygiene and Public Health. To receive his public health doctorate, he must have been commuting between Detroit, Michigan, and Baltimore, Maryland. Did Ramsey consult Frost about the Flint outbreak? Frost esteemed Ramsey and, in 1926, hired him as an associate professor. An anecdote bespeaks of Frost and Ramsey’s later closeness: Frost’s wife, to tease the “exceptionally shy, bachelor, faculty member,” once served Ramsey a rubber hot dog at a dinner at the Frosts’ home (15, pp. 122–123). Thus, Frost could plausibly have advised Ramsey during the Flint investigation and then refused to coauthor his student’s paper, as he usually did. Was the Flint study Ramsey’s unknown dissertation topic? The weakness of this interpretation is that Frost did not design other case-control studies, and he still carried out surveys in the late 1920s in situations where case-control studies would have been the superior choice (25).

The discovery of Ramsey’s study does not shake the common beliefs about the history of case-control studies. Their main roots plunge into the epidemiology of cancer and coronary heart disease (6, 7). Cases of these rare diseases were concentrated in hospitals and medical practices. Identifying controls among people who were free of cancer or of coronary heart disease was the optimal comparative option, particularly because cohort studies (an older study design) would have had very low statistical power. Still, in keeping with the epidemiology-as-archaeology analogy, Ramsey’s study is evidence of an interrupted branch on the phylogenetic tree of case-control studies, because, amazingly, its design had no direct sequel. The paper apparently fell into oblivion, at least as a case-control study (the only citations I know are by Godfrey (26) and Comstock (27)). In contrast to the chronic disease evolutionary branch, which is richly populated, there is for now no clear path leading from 1924 Flint to 1940 Lyonning, Oswego County, New York, where a case-control study identified vanilla ice cream as the culprit of a gastroenteritis outbreak (28, 29). The lack of attention given by research
centers in America and Europe to this innovative report is remarkable and suggests that the Michigan Department of Health hit upon the new design independently. On the other hand, Ramsey, studying epidemiology at Hopkins, could have been exposed to the ideas then being practiced in England by Lane-Claypon and Major Greenwood. A less speculative explanation for the conception of Ramsey’s study remains elusive at present.

In conclusion, George H. Ramsey and the Michigan Department of Health deserve recognition for at least 2 historical contributions: 1) They established the causal role in scarlet fever transmission of one of today’s main vectors of bacterial epidemics, ice cream; and 2) they conducted and reported results from the as-of-yet oldest, undisputable case-control study in the epidemiologic literature. Flint, Michigan, the cradle of General Motors and of recognized labor unions in the United States, appears to have also been a birthplace of case-control studies.

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