Mantel, Nathan

Born: February 16, 1919 in New York City, New York.
Died: May 26, 2002 in Potomac, Maryland.

Nathan Mantel, pioneering biostatistician, and author of more than 380 published articles, was born in New York City to Polish and Hungarian immigrants, Rose Steinberg and Hyman (Nehemiah) Mantel. Nathan was the middle child between two sisters, Ray (Rifka, born 1917) and Anne (Channa, born 1920). Like many Jewish immigrants at the time, Nathan (Naftoolyah) grew up on the lower east side of New York City in tenement housing. He was raised poor, speaking Yiddish at home and at Hebrew School, but speaking and writing in English at his public school [11]. During the great depression, his Judaic studies took a turn away from the Orthodox Judaism of his parents when he and his sisters began residence in the Hebrew Orphan Asylum at 137th Street, Amsterdam Avenue. This unassuming orphanage provided safe harbor for many other future notables. Also in residence were Art Buchwald (syndicated columnist), Aaron L. Jacoby (politician), Dr. Herman Schwartz (biologist), Harold Tovish (sculptor), and many others [2]. During his adolescence, Nathan's maternal grandparents and 11 aunts, who had all remained in Eastern Europe instead of immigrating to the United States, were killed in the holocaust. Many of his paternal relatives immigrated to America successfully.

Nathan's academic training began at New York City's Stuyvesant High School. This premier school for science and mathematics helped to cultivate Nathan's interest and ability in mathematics, though his mature interest did not manifest itself until much later in his life. By most accounts, he was only a mediocre student [11]. However, even in high school, he participated in mathematics competitions. In his senior year, he derived a novel way to solve the Diophantine equation ($ax - by = c$), which was later published in the *American Mathematical Monthly* [7]. This would be the first of his numerous publications. In 1939, he graduated from City College of New York with a major in statistics. At City College, he took courses with other future statisticians, including Marvin **Schneiderman** and Bernard **Greenberg**. He later went on to earn a Master's degree in statistics from American University in 1956, already having published twenty-one articles in the field.

His career as a professional statistician began in 1940, after a series of low-level federal jobs. At this time, Nathan was recruited into what later became the War Production Board, where his skills helped increase the output of the nation's factories. Later, a portion of his World War II military service in the Army Air Force involved statistical analysis of medical research. But, with the war's end, the agency closed down and Nathan, who at that time was living with his family in temporary government housing in what is today the National Park Service's Kenilworth Aquatic Gardens, was jobless.

In 1947, Mantel went for a job interview at the National Cancer Institute (NCI) in the **National Institutes of Health** (NIH). He was quickly hired by Harold **Dorn** as a member of a new biometry group and set to work with such biostatisticians as Jerome **Cornfield**, Samuel **Greenhouse**, Jacob Lieberman, and Marvin Schneiderman (an old college pal of Nathan's). The rest, as they say, is history. Of this time period, Sam Greenhouse wrote, "... among statisticians the world over, we had probably the greatest artist of all – Nathan Mantel. No one could match him in quickly identifying the information in the data related to the questions and the swiftness with which he was able to choose an optimum method of analysis. The statistical procedures which bear his name are really nothing compared to his ability to analyze data. The former would have eventually been derived by others, but it is doubtful whether anyone else has had his intuition" [5].

In the field of biostatistics, Nathan Mantel has published papers on leukemia, lung cancer, Down's syndrome, chemotherapy, breast cancer, passive smoking, vehicle emissions, and much more. Most notably, he developed the **Mantel–Haenszel** procedure and its extensions. William **Haenszel**, who had been working on interpreting the **case–control studies** of the connection between **smoking** and lung cancer, requested Mantel's assistance on how to analyze the retrospective data. Mantel then collaborated with Haenszel on a paper that aimed to reach the same conclusions "in a retrospective study as would have been obtained from a forward study, if one had been done" [10]. Their highly cited paper, "Statistical Aspects of the Analysis of Data from Retrospective Studies of Disease", [10] presents the Mantel–Haenszel procedure, which provides a summary estimate of the exposure effect stratified by multiple sources (i.e. different studies) or **confounding** factors (such as age and sex), which is a weighted average of the **odds ratios** across various strata.

The applications and extensions of this procedure are many. Since this test allows for combining data from different sources, it can be used in a variety of contexts: retrospective studies, prospective studies, and laboratory experiments, including those with litter-matched samples. Mantel used the procedure to develop the first version of the **logrank test**, a test that compares **censored** time-to-response distributions [8], and later extended the test to the evaluation of response time data involving transient states [9]. These important applications contributed greatly to the development of **survival analysis** [4]. Mantel notes about his 1959 paper: "It turned out that the procedures in the paper could be extended so that they met perhaps 90 to 95 per cent of the kinds of problems that people were encountering" [6].

In addition, Mantel offered abundant insights to both **epidemiology** and laboratory research: He demonstrated that a prospective logistic risk model can be used to analyze case–control data [6]. He also explored the distribution of cancers among related diseased pairs to test whether the cause of the cancer was due to environmental exposure in addition to hereditary factors [4]. Further, Mantel developed methods to investigate temporal and spatial **clustering** of diseases such as polio, hepatitis, and childhood leukemia [4]. In 1961, Nathan devised the Mantel–Bryan approach to test for safety of carcinogenic agents (*see* **Tumor Incidence Experiments**). His definition of a "virtual safe" dose as a risk of one per 100 million or less was used by the **Food and Drug Administration** for several years before the standard was adapted to a less conservative definition of "safety" at one per million or less [6]. He later commented in an EPA Watch newsletter about the arbitrary nature of the original standard: "We just pulled it out of a hat" [1]. Upon hearing that a bureaucrat had dropped two zeros from his standard of one per 100 million, Nathan is reported to have remarked, "Well, that's government science for you!" Describing his overall approach to problem solving, Mantel wrote, "I generally don't generate ideas of my own. Someone has to come to me with a problem. And, apparently, I'm pretty good at coming up with solutions or ideas for solutions. Identifying problems is what is important – solutions just follow." [3].

A recipient of many professional honors, after retiring from the NCI, Mantel served as a research professor at George Washington University and later at American University. He was a visiting scientist at the New York University School of Medicine, a visiting professor at the University of Tel Aviv, and a visiting professor in neuroepidemiology at Temple University School of Medicine. He was also a lecturer at the China National Center for Preventive Medicine in Beijing. At its 2002 Annual Meeting, the **American Statistical Association** announced the establishment of the Nathan Mantel Lifetime Achievement Award for statisticians who have made significant contributions to the field of biostatistics over their careers. Nathan did not live to see the presentation of this award, as he died in his sleep on May 26, 2002. The epitaph on his gravestone reads, "One in a million", which serves as a concrete reminder of his lasting contributions to statistics and public policy. For additional biographical information and summaries of Nathan's work, refer to [2–6, 11].

References

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Mantel–Haenszel Methods

Biomedical, clinical, patient-oriented, and public health research investigations frequently focus on the relationship between a primary **factor**, such as an exposure, a new therapy, or an intervention, and a **response variable** such as disease classification, functional status, or degree of improvement. When both of these variables are reported on categorical data scales, the resulting data typically are summarized as observed frequencies in a two-way **contingency table**. However, this *factor–response* relationship may be influenced by other *covariables* or **covariates**, such as clinical centers or baseline characteristics. Consequently, appropriate adjustments for these covariables must be incorporated into the data analysis.

The historical review of Mantel–Haenszel methods outlined in this article is drawn heavily from the extensive review article by Kuritz et al. [34]. In a classic paper, Cochran [13] proposed a test for several **two-by-two tables** based on **binomial** model assumptions. Five years later, Mantel & Haenszel (MH) [46] approached this same problem using a **hypergeometric** probability model, which permits either exact tests or requires only the overall sample size to be large for asymptotic results to hold. The resulting test statistics from these two procedures are nearly identical, except for applications in which the within-table sample sizes are sparse. In particular, the MH test statistic is entirely appropriate for within-table sample sizes as small as two, provided that there are enough tables. Birch [5] demonstrated that when within-table **odds ratios** are homogeneous, the MH test statistic is the uniformly **most powerful** unbiased (UMPU) test. Also, it is asymptotically equivalent to specific likelihood ratio (LR) tests from unconditional **logistic regression** when within-table sample sizes are large, and to specific LR tests from **conditional logistic regression** when within-table sample sizes are small [9].

Mantel–Haenszel (MH) procedures are most useful to test H_0: "no partial association" against alternatives encompassing an average effect of the *factor* on the *response* across strata based on the set of *covariables*. In many situations, the sample sizes for some tables may be sparse, the magnitude of the partial association may vary across tables, and the association may be small within subtables. However, if the association is slight, but consistent across the tables, MH procedures will be effective in detecting that association.

Perhaps the most important distinguishing feature of the MH procedures are their connections to randomization model considerations. Quite frequently, health research data are collected under observational study designs such as **case–control studies**, or convenience sampling for a randomized, **multicenter** efficacy trial. For such situations, MH procedures provide a randomization, design-based approach to **hypothesis testing**. These methods require no assumptions other than the **randomization** of subjects to factor levels, either explicitly as in randomized controlled **clinical trials**, or implicitly by hypothesis or from conditional distribution arguments for observational data from restrictive populations such as **retrospective studies**, nonrandomized **cohort** studies or case–control studies [30, 35].