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A Conversation with Fred Ederer

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Abstract. Fred Ederer was born on March 5, 1926, in Vienna, Austria. He received a B.S. degree in mathematics and science from the City College of New York, an M.A. degree in statistics from American University and did further graduate work in biostatistics at Columbia and Stanford Universities. He is a Fellow of the American Statistical Association, of the American College of Epidemiology and of the American Heart Association's Council on Epidemiology. He has been on the editorial boards of the *American Journal of Ophthalmology*, *Survey of Ophthalmology* and the *American Journal of Epidemiology.* He has served on the Council on Epidemiology, the American Heart Association and the Regional Advisory Board of the Eastern North American Region of the Biometric Society, and he was on the Founding Board of Directors for both the Society for Clinical Trials and the American College of Epidemiology. His tenure at the National Institutes of Health (NIH) included the years 1957 through 1986. He began at the National Cancer Institute, moving next to the National Heart Institute and then spending the next half of his NIH career at the National Eye Institute (NEI). His first position at NEI was as Head of the Section on Clinical Trials, then Chief of the Office of Biometry and Epidemiology and, finally, Associate Director for Biometry and Epidemiology. He was awarded the Superior Service Award, one of the highest civilian awards given at NIH. Since leaving NIH, he has been Senior Epidemiologist at the EMMES Corporation and Adjunct Professor in the Division of Biostatistics at the University of Minnesota.

Green: What were you doing before you came to the National Institutes of Health (NIH) and how did you get recruited to NIH?

Ederer: I came to the NIH in January of 1957. Before coming to Washington, I worked at the New York City Health Department. My first position in Washington was in the Office of the Surgeon General of the Air Force, after which I was at the Bureau of Labor Statistics (BLS).

While at the BLS, I was also taking graduate courses in the Department of Statistics at the American University. I remember vividly a one-year course in biometrics taught by Jerry Cornfield (there were several people from the NIH in the course). It was the most fascinating course I ever had in college or graduate school. It was a very lively class, with Cornfield starting each evening session with a statistical problem either from his own experience or from the literature. He threw the problem out to the class, and a lively discussion ensued. Some of the problems included the toxicity of the Salk vaccine, and the association of smoking and lung cancer. He was a very entertaining lecturer and an outstanding teacher. He even laughed at his own jokes. After I joined the BLS I decided that labor statistics was not for me. I was very attracted to the NIH, and I really wanted to get back to medical statistics. I had had several interactions with Marvin Schneiderman and Nathan Mantel, and had very lively discussions with a lot of give and take. Cornfield arranged for an interview for me with Sid Cutler, who headed up the End Results Section in the Biometry Branch at the National Cancer Institute (NCI). Sid hired me and also John Bailar, who came into the program just about the time I did.

Michael Shimkin, a physician, was Chief of the Biometry Branch, with Bill Haenszel as Deputy

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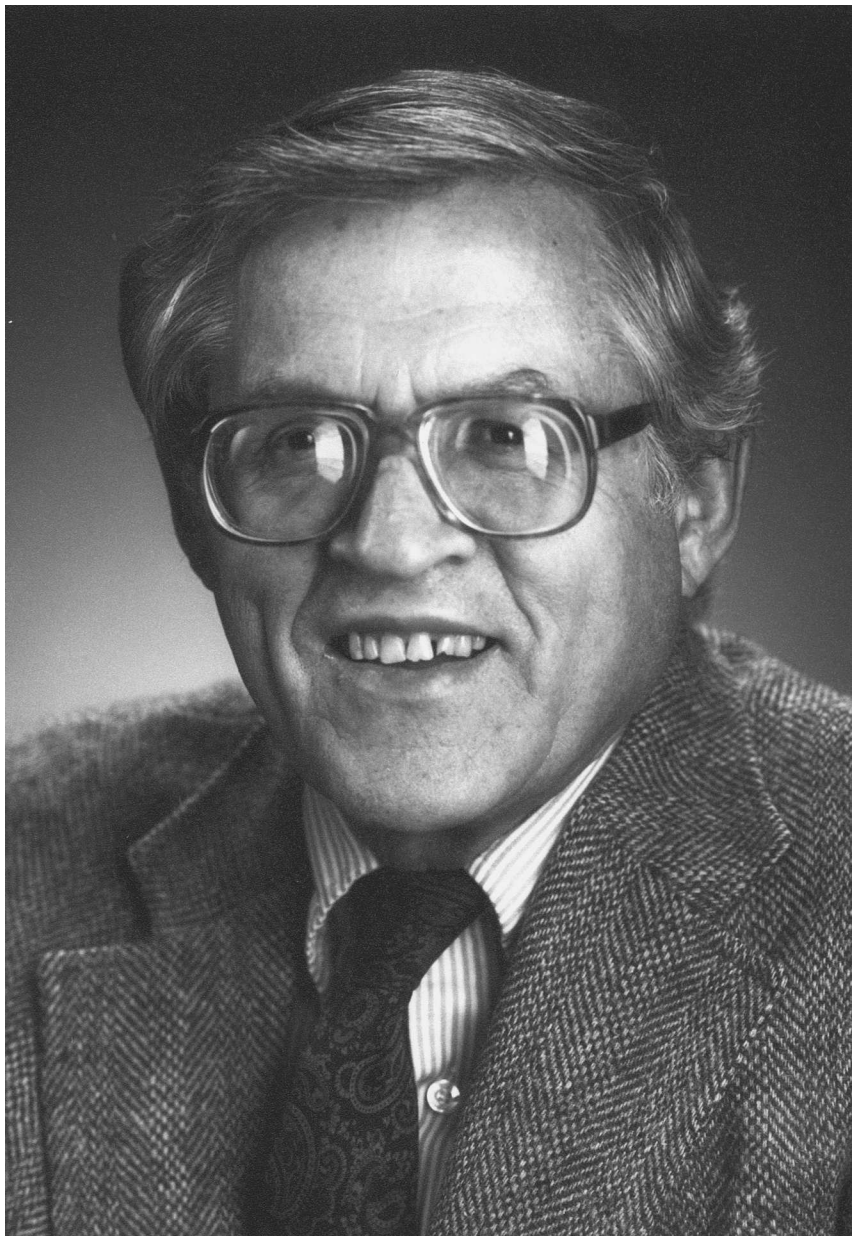

FIG. 1. *Fred Ederer.*

Branch Chief. In addition to Sid Cutler's End Results Section, the Branch included Marvin Schneiderman as Head of the Clinical Trials Section, and Nathan Mantel as Head of the Experimental Statistics Section.

Green: Was there a lot of interchange among the statisticians?

Ederer: No, we didn't work together officially (except people within a Section), but most of the statisticians from all Institutes met at lunch. There were not that many statisticians at the NIH at the time, and most of them were in the NCI. When I arrived at NIH, Jerry Cornfield and Harold Dorn were administratively located in a biometrics branch within NIH, but not in one of the categorical Institutes. Felix Moore headed up a biometry group in the Heart Institute. Max Halperin was in the Division of Biologic Standards. Sam Greenhouse was with the Mental Health Institute. Seymour Geisser came in shortly after I did, to work with Sam Greenhouse in the Mental Health Institute. Most of these statisticians would show up at least once a week, if not more often, at the lunch table. The luncheon discussions were always lively, sometimes passionate, whether they pertained to politics, statistics or any other subject. I recall Mantel and Halperin most frequently disagreed. Cornfield did not get himself deeply entrenched in these arguments, though. He stayed above the fray most of the time.

Green: Was one person considered senior among the group or was this really a group of equals?

Ederer: In those days everyone looked up to Jerry Cornfield. He was the leader, by virtue of his very sharp intellect and his forceful arguments, and he was also older than most of us.

Green: How would you describe the general atmosphere at NIH in those days? How did it differ from more recent times?

Ederer: I'm not sure that there has been a lot of change in atmosphere. There has always been a lot of academic freedom. If people were unhappy with a project, they did not necessarily have to work on it. There were so many things to do, that people could choose their preferred work. This might have changed a little bit over time.

Green: What was your employment chronology at NIH?

Ederer: I was at NIH for 29 years. I spent 7 at the Cancer Institute, 7 at the Heart Institute and 15 at the Eye Institute. My moves corresponded to other changes in the statistical staffing at NIH. Harold Dorn had started out in the National Cancer Institute in the early 1950s. In the mid-1950s Dr. James Shannon, the then Director of the National Institutes of Health, asked Dorn to move out of the Cancer Institute to more neutral ground, so that he and several other people (which included Cornfield) would be able to provide some statistical services to Institutes which did not have statisticians. They were also to help these other Institutes set up programs in statistics. By 1960 Dorn felt that these objectives had been accomplished. Felix Moore had left the statistics program in the Heart Institute for the University of Michigan, and Harold Dorn took over the Heart Institute program. Cornfield moved with him. Dorn died fairly suddenly in 1962, and Jerry Cornfield became the Branch Chief. In a subsequent meeting with Jerry Cornfield, he told me there was an opening in the Heart Institute. I was offered and accepted the position there in 1964. Although I gained a lot of good experience at the Cancer Institute and thought it had been very productive (I had then been at the NCI for seven years), I also thought it was time to enter into a new disease area. I stayed at the Heart Institute for seven years.

I then joined the National Eye Institute (NEI) in 1971, in the first year of its existence. Harold Kahn, who was with me at the National Heart Institute, had accepted a position as Chief of the Biometry and Epidemiology Branch at NEI, and he almost immediately offered me a position.

Green: In the early days, back when you first started in the National Cancer Institute, what was the status of clinical trials?

Ederer: It wasn't really until the late 40s that randomized clinical trials (RCT's) were done. Bradford Hill in England pioneered these studies. His landmark paper reported the results of a streptomycin trial in tuberculosis [22]. By the mid-1950s some RCT's were being done in the United States, primarily in the cancer–chemotherapy field. There was a mid-1950s study in retrolentalfibroplasia, and, interestingly enough, Bradford Hill had been a consultant to the study. I came to the National Cancer Institute in 1957 just when Congress gave a large sum of money to the NCI for developing and testing chemotherapeutic agents. It was a huge program, with Marvin Schneiderman at the helm of the clinical trials program. Gradually, other clinical trials groups and statistical centers for cancer clinical trials began to form.

There were also trials going on in Mental Health, including chemotherapy trials. Sam Greenhouse was involved in those. I am not aware of clinical trials back in the 1950s in any other disease areas. There was still a lot of resistance by physicians to randomization at the time. It was a new concept for many of them. Jerry Cornfield and Lincoln

Moses as the statisticians for a radiotherapy group in lung cancer spoke about randomization, but the ideas were not readily accepted. Thus, one of the significant activities in the early days was teaching clinical investigators about RCT's. When I came to the Eye Institute most of the clinicians working in the eye field didn't know about randomized trials, or if they did they were not accepting of them. So we pioneered clinical trials in eye disease. Again, as in the cancer field, it was a matter of teaching people both the rationale and the mechanics of doing RCT's.

Green: How did the rest of the NIH community interact with the statisticians?

Ederer: I think where there was strong medical leadership in the NIH that understood the role of statisticians, the statisticians were used. Where the leadership was lacking, they were not used. An example of that was Michael Shimkin, as the Biometry Branch Chief in the Cancer Institute. He was a very forceful leader, and well respected by cancer researchers throughout the country, as well as at the NIH. He exerted a lot of positive influence in that regard for the inclusion of statisticians on projects. Shimkin, at an address he made at the Third National Cancer Conference in Minneapolis in 1960, talking about the role of statisticians, said, "We have learned of the need for unequivocal definitions and criteria for meticulous experimental designs, of the requirement for randomized controls, and of the innumerable sources of bias that can be avoided by double-blind techniques, of the placebo effect to which the investigator is as liable as the subject, and of the annoying biostatistician who questions our plans, makes impossible demands, and finally doubts our interpretation of the results."

Green: You mentioned that when you were first at the National Eye Institute they did not have any clinical trials; yet over the years they developed major, large randomized trials.

Ederer: Yes, and we owe this to the Director of the National Eye Institute, Carl Kupfer, who was there since its creation. He made clinical trials a high priority. He understood the importance of statistical input and he urged the statisticians to play leadership roles, which we did. We taught courses and we played an active role in getting trials started, especially the early studies. We brought in ophthalmologists who learned about biometry and epidemiology. They became leaders in the field.

Green: What would you say were the key events that really helped statistics get established as a recognized discipline at NIH?

Ederer: I can cite three things: first, the development of clinical trials that involved statisticians. I think the community recognized that statisticians played an important role in this area [4, 8]. A second area was the field of epidemiology. In that field people like Harold Dorn, Bill Haenszel, Nathan Mantel and Jerry Cornfield were very productive and visible. They made major contributions particularly in the area of case–control studies (or retrospective studies as they would have been called), but also in prospective studies, or cohort studies. Harold Dorn himself conducted one of the landmark studies of U.S. veterans, or policyholders of U.S. Veterans Insurance in his lung cancer study [18]. Because of the early leads from the Dorn studies, suggesting a relationship between lung cancer and smoking, case–control studies were started. But at that time case–control studies really lacked theoretical foundation, and the theoretical foundation for these studies was evolved by Cornfield, Dorn, Haenszel and Mantel. This was a landmark development and an outstanding contribution made by NIH statisticians.

The third area was laboratory consultation. I was not involved in those, but people like Cornfield and Mantel were in Cancer [3, 6]; and in biologic standards, Max Halperin; and in the mental health field, Sam Greenhouse. Biostatisticians played an active role but no landmark event occurred in that field. Some laboratory scientists recognized the need for statistical collaboration, and they sought it out. Others did not recognize it and they did not seek it out. And, I suspect this is still true to the present day.

Green: Which of your collaborations led to research on statistical methodology?

Ederer: One of the methodologic issues that arose from a collaborative effort involved cancer clusters. There were no statistical methods at that time for evaluating cancer clusters. So, I worked with Max Myers and Nathan Mantel on a method, and after that numerous other methods were developed [15].

Another example came from the analysis of data from the End Results Program [the predecessor of the current Surveillance, Epidemiology and End Results (SEER) program]. We were collecting massive amounts of survival data from a number of cancer registries and we were faced with the problem of analyzing and interpreting the data. We were concerned with life table methods [7]. The notion of both observed rates and expected rates was introduced, where the expected rates came from the general population life table. We examined the concept of relating one to the other in terms of the relative rate. Sid Cutler and I did some exploratory work in this area [14].

Green: What were some of the most important methodologic results that demonstrate the contributions of statistics to the work at NIH.

Ederer: Based on my own experience, I think the two most outstanding methodologic contributions were the developments in clinical trials methodology and in case–control studies. The NIH statisticians essentially wrote the textbook for case-control studies back in the late 1950s and early 1960s [5, 21]. Although later developments [20, 25, 26] have taken the case–control study further, the basic book was written at that time. I think this was recognized at the time, but it became reinforced as the passage of time provided historical perspective. Disease clustering methodology was another important area of contributions developed at the NIH.

Green: When these various statistical issues came up, did you have the freedom to pursue the methodologic aspects?

Ederer: There were no constraints. That kind of work was encouraged at the time. Something always came along that just had to be done; so there was not a hundred percent freedom, but there was a considerable amount of freedom in the way we chose what to work on.

Green: What would you cite as some of the strengths of the NIH environment that allowed it to be so productive?

Ederer: In addition to the considerable amount of academic freedom to pick and choose what you wanted to work on, the other important factor was the large number of talented people at the NIH, as there still are today (not only in statistics, but in other fields as well). There was a climate of excellence, and there were people to talk to, people to discuss things with, people you could collaborate with. You could find expertise in areas that you might not have had yourself; I think these traditions have been maintained over the years.

Green: Were there major studies or major findings that came out of NIH research where the statisticians were really the prime players?

Ederer: In the cancer field prominent substantive contributions were made by Harold Dorn, Bill Haenszel, Sid Cutler and Nathan Mantel. Harold Dorn in his study of veterans (a study of some 200,000 veterans) produced a major finding of a 10-fold increase in lung cancer risk for cigarette smokers [11, 12]. That was one of the two most important studies that were done on that subject, the other one being of British doctors by Doll and Hill [10]. There were also many case–control studies done shortly after those findings were made public. Mantel and Haenszel did a case–control study of lung cancer in women [17], and Jerry Cornfield was involved in some case–control studies of lung cancer also [24, 27]. Bill Haenszel did a number of migrant studies. One of them he started with Harold Dorn, and they became leaders in the field of migrant studies. For example, in a study of British and Norwegian migrants in the United States, the question was whether the morbidity and mortality experience of these migrants was the same or different from their siblings who remained behind them in their mother country [23].

Another area is the series of National Cancer Surveys. These incidence surveys were done around 1940, 1950 and after that, I think around the 1970s [9]. The people involved were Harold Dorn, Sid Cutler, Bill Haenszel and John Bailar.

In the Heart Institute a major activity was the Framingham Heart Study. Statisticians played leadership roles from the beginning. It was Felix Moore to start with. Tavia Gordon was also involved very early. There were also some studies that were sponsored by the Heart Institute, similar to Framingham, but outside the United States. Harold Kahn spent three years in Israel and played a prominent role in a study among Israeli civil servants of risk factors for cardiovascular disease.

Green: Was there an interest in Bayesian approaches at NIH?

Ederer: Yes, in the 1960s when the Heart Institute got started with clinical trials. Jerry Cornfield became dissatisfied with the frequentist approach to clinical trials, and became a Bayesian. He published numerous papers on that subject [1, 2]. As forceful a leader as he was, there were not many people who became persuaded by his arguments, and although some Bayesian methods were used in the trials in which he participated, they were peripheral. The main conclusions were based on frequentist methodology. Thirty years later, there is an increased interest and application of Bayesian methodology in clinical trials.

I was always sympathetic to a Bayesian approach. I thought that it had some strengths, and I agreed with Cornfield that the frequentist approach has weaknesses. Perhaps there is a place for both kinds of methodology. Among the Heart Institute statisticians who were strong opponents of the Bayesian approach was Max Halperin. Max did not have much use for Bayesianism.

Green: Was Cornfield a strong supporter of randomized trials?

Ederer: Absolutely. He was as strong a supporter of randomized trials as anyone I know [13]. But at the same time, he did not have the extreme view that some statisticians held: that if the study could

not be done with randomization, it was of no use. Cornfield had a very different approach. He recognized that randomization could not be applied to all scientific endeavors—and that many disciplines had progressed without randomization, such as astronomy and geology to name two.

Green: What were the feelings of the rest of the statisticians at NIH about randomization?

Ederer: My sense was that the statisticians, by and large, believed that where randomization was feasible it should be done. I don't know of anyone who would quarrel with that. And, I think most people recognize that it could not be done in all situations, that observational studies had to be done to elicit information in some areas.

Green: What were the major involvements of statisticians in the Eye Institute.

Ederer: My major involvement at the Eye Institute in its early days (in the 1970s) was as a teacher and leader, if you will, in the clinical trials area. Harold Kahn took on the epidemiology area, and he started the Framingham Eye Study. This was an eye survey of survivors of the original Framingham Heart Cohort, which had been started about 1950. Here, 20 years later, Harold Kahn came in and with the ophthalmology group at Boston University did an eye survey. That was a pioneering effort in the epidemiology of eye diseases led by a statistician [19].

Green: In the field of ophthalmology, where there have been a number of large randomized multi-center trials, what role did the statisticians at NIH play in seeing that those were implemented.

Ederer: With encouragement from the Director of the National Eye Institute, Dr. Carl Kupfer, the biometry group played a very important role. Our group conducted a workshop on randomized trials at a meeting of the American University Professors of Ophthalmology, where the whole concept of randomized trials was introduced. Initially, there was resistance by some of these professors to the whole idea of randomization. They had done their previous studies without randomizing. But eventually randomization became accepted. The Biometry group at the Eye Institute taught a course initially at the annual meetings of the Academy of Ophthalmology, and later just before the annual meeting of the Association for Research on Vision and Ophthalmology (ARVO). The early course was only a few hours, but the later course was about $2\frac{1}{2}$ days. Every year about 60 people were enrolled in it, and we taught the course in Florida (preceding ARVO) for 11 consecutive years. Many people took the course, entitled "Clinical vision research: biostatistical and epidemiologic approaches," and learned how to do clinical trials. Of course, participants in the ongoing multicenter trials learned how to do them also. While staff at the Eye Institute started several of the multicenter trials during the 1970s, the researchers in the community were eventually encouraged to apply for grants, and the initiatives reverted to the research community at large.

Green: When you left the NIH in 1986, with what thoughts did you look back over your time at NIH?

Ederer: Always with a great deal of satisfaction and gratification. I view my years spent at the NIH as wonderful years. I felt that I was getting paid for doing something that I enjoyed doing. I think the NIH statistical community continues to thrive, and there still exists an atmosphere of excellence to the present day.

Green: Your description of the crowd when you first came to NIH indicated something very special about the interactions of that group, that it was a unique combination of people.

Ederer: Yes. I think what also distinguished that group of statisticians is that it was a small group. When I first came to NIH the number of statisticians may have been between 10 and 20. Most of us knew each other and met for lunch. That, of course, is no longer true. There are now well over a hundred statisticians scattered in buildings on and off campus at the NIH, and many of them don't know each other at all.

Green: What role did the early group of statisticians at NIH play in training?

Ederer: There was teaching by NIH statisticians at American University, George Washington University and the University of Maryland. That continues to some extent today. But I think the major influence that the senior statisticians had for junior statisticians at the NIH came at the NIH itself. During the 1950s and 1960s there was an active seminar program (there were monthly biostatistics seminars). For a number of years I managed those. Working side by side with the senior statisticians was a very important learning opportunity for the younger statisticians.

Green: Do you feel that there were a lot of people who came through for short terms of experience at NIH, who were really influenced by their time at NIH?

Ederer: Well, it is certainly true that many of the statisticians who worked with me at the NIH rose to prominent positions and to recognition after they left the NIH. I can think of Marvin Zelen, John Bailar, Polly Feigl, Seymour Geisser, as examples. These were, certainly, talented people to begin with, and you can't give the NIH all the credit for

their success. But I am sure that the NIH experience was a positive one and did play a role in their development.

Green: Is there anything else about the NIH that made it special?

Ederer: The NIH over the years has maintained an environment of excellence in science. That is certainly true in statistics, and I am sure it is true for other fields as well. In the field of statistics that environment of excellence was started by Harold Dorn, who single-handedly hired, just in his first few years, Jerome Cornfield, Sam Greenhouse, Marvin Schneiderman, Nathan Mantel and Sid Cutler. These were outstanding people. How he was able to find them and select them, I don't know; but, he did. I think the fact that he got off to this wonderful start made it easier for the NIH to maintain the tradition of excellence over the years.

Green: As a distinguished NIH alumnus, do you have any advice for the NIH biostatistical community?

Ederer: I don't think they need any advice. The NIH statisticians are really doing well as demonstrated by the quality of the conference on "Current Topics in Biostatistics" that was held in January of 1993 [16]. The tradition of excellence is deeply rooted and has been maintained, and I think it will continue to be maintained over the years.

REFERENCES

[1] CORNFIELD, J. (1966). A Bayesian test of some classical hypotheses—with applications to sequential clinical trials. *J. Amer. Statist. Assoc.* **61** 577–594.

[2] CORNFIELD, J. (1969). The Bayesian outlook and its application. *Biometrics* **25** 617–657.

[3] CORNFIELD, J., GORDON, T. and SMITH, W. W. (1961). Quantal response curves for experimentally uncontrolled variables. *Bulletin of the International Statistical Institute* **38** 97–115.

[4] CORNFIELD, J. and GREENHOUSE, S. W. (1965). On certain aspects of sequential clinical trials. *Fifth Berkeley Symp. Math. Statist. Probab.* 813–829. Univ. California Press, Berkeley.

[5] CORNFIELD, J. and HAENSZEL, W. (1960). Some aspects of retrospective studies. *Journal of Chronic Diseases* **11** 523–534.

[6] CORNFIELD, J. and MANTEL, N. (1950). Some new aspects of the application of maximum likelihood to the calculation of the dosage response curve. *J. Amer. Statist. Assoc.* **45** 181–210.

[7] CUTLER, S. J. and EDERER, F. (1958). Maximum utilization of the life table method in analyzing survival. *Journal of Chronic Diseases* **8** 699–712.

[8] CUTLER, S. J., GREENHOUSE, S. W., CORNFIELD, J. and SCHNEIDERMAN, M. A. (1966). The role of hypothesis testing in clinical trials. Biometrics seminar. *Journal of Chronic Diseases* **19** 857–882.

[9] CUTLER, S. J. and YOUNG, J. L., JR. (1975). Third National Cancer Survey: incidence data. In *National Cancer Institute Monograph* **41** 1–45.

[10] DOLL, R. and HILL, A. B. (1956). Lung cancer and other causes of death in relation to smoking. A second report on the mortality of British doctors. *British Medical Journal* **2** 1071–1081.

[11] DORN, H. F. The mortality of smokers and non-smokers. In *Proceedings of the Social Statistics Section* **1** 34–71. Amer. Statist. Assoc., Alexandria, VA.

[12] DORN, H. F. (1959). Tobacco consumption and mortality from cancer and other diseases. *Public Health Reports* **74** 581–593.

[13] EDERER, F. (1982). Cornfield's contributions to the conduct of clinical trials. *Biometrics Suppl.* **38** 25–32.

[14] EDERER, F., AXTELL, L. M. and CUTLER, S. J. (1961). The relative survival rate. A statistical methodology. In *End Results and Mortality Trends in Cancer. National Cancer Institute Monograph* **6** 101–121. U.S. Department of Health Education and Welfare, Public Health Service, National Institutes of Health, National Cancer Institute, Bethesda, MD.

[15] EDERER, F., MYERS, M. H. and MANTEL, N. (1964). A statistical problem in space and time. Do leukemia cases come in clusters? *Biometrics* **20** 626–638.

[16] ELLENBERG, J. H., GAIL, M. H. and SIMON, R. M., eds. (1994). National Institutes of Health Conference on Current Topics in Biostatistics. *Statistics in Medicine* **13** 399–783.

[17] HAENSZEL, W., SHIMKIN, M. B. and MANTEL, N. (1958). A retrospective study of lung cancer in women. *Journal of the National Cancer Institute* **21** 825–842.

[18] KAHN, H. A. (1966). The Dorn study of smoking and mortality among U.S. veterans: report on eight and one-half years of observation. In *National Cancer Institute Monograph* **19** 1–25.

[19] KAHN, H. A., LEIBOWITZ, H. M., GANLEY, J. P., KINI, M. M., COLTON, T., NICKERSON, R. S. and DAWBER, T. R. (1977). The Framingham Eye Study. I. Outline and major prevalence findings. *American Journal of Epidemiology* **106** 132.

[20] MANTEL, N. (1973). Synthetic retrospective studies and related topics. *Biometrics* **29** 479–486.

[21] MANTEL, N. and HAENSZEL, W. (1959). Statistical aspects of the analysis of data from retrospective studies of disease. *Journal of the National Cancer Institute* **22** 719–748.

[22] Medical Research Council (1948). Streptomycin treatment of pulmonary tuberculosis. *British Medical Journal* **2** 769–782.

[23] REID, D. D., CORNFIELD, J., MARKUSH, R. E., SEIGEL, D., PEDERSEN, E. and HAENSZEL, W. (1966). Studies of disease among migrants and native populations in Great Britain, Norway, and the United States. 3. Prevalence of cardiorespiratory symptoms among migrants and native-born in the United States. In *Epidemiological Approaches to the Study of Cancer and Other Chronic Diseases. National Cancer Institute Monograph* **19** 321–346.

[24] SADOWSKY, D. A., GILLIAM, A. G. and CORNFIELD, J. (1953). Statistical association between smoking and carcinoma of the lung. *Journal of the National Cancer Institute* **13** 1231–1258.

[25] SEIGEL, D. C. and GREENHOUSE, S. W. (1973). Multiple relative risk functions in case–control studies. *American Journal of Epidemiology* **97** 324–331.

[26] SEIGEL, D. C. and GREENHOUSE, S. W. (1973). Validity in estimating relative risk in case–control studies. *Journal of Chronic Diseases* **26** 219–225.

[27] WYNDER, E. D. and CORNFIELD, J. (1953). Cancer of the lung in physicians. *New England Journal of Medicine* **248** 441–444.