Profiles in Medical Courage: Causation and Austin Bradford Hill

"The secret language of statistics, so appealing in a fact-minded culture, is employed to sensationalize, inflate, confuse, and oversimplify"
-Darrel Huff in *How to Lie with Statistics*

Abstract

Austin Bradford Hill was a British epidemiologist and statistician who is best remembered for two landmark pulmonary studies. He was the statistician on the Medical Research Council Streptomycin in Tuberculosis Trial. This is regarded as the first randomized clinical trial. The second was the demonstration of the connection between cigarette smoking and lung cancer. However, Hill's most lasting contribution may be his establishment of a group of conditions necessary to provide adequate evidence of a causal relationship between an incidence and a consequence, widely known as the Bradford Hill Criteria of Causation. In this profile of medical courage we examine his remarkable background that led to the epidemiological equivalent of Koch's postulates.

Introduction

Recently, two articles have appeared in the *Southwest Journal of Pulmonary and Critical Care* which involved Sir Austin (Tony) Bradford Hill. The first was Dr. Raschke's review of Doll and Bradford Hill's landmark study on the etiology of lung cancer (1). The second was the prior profile in medical courage article on Archie Cochrane, Bradford Hill's student (2). These prompted me to conduct a study of Bradford Hill and his remarkable career. Although both of his studies are important, his criteria for causation may be his greatest legacy (3). In a time when the unscrupulous utter half-truths to associate an incident with a consequence, Bradford Hill's criteria for causation are as relevant today as they were when first published in 1965 (3).

Early Life

Austin Bradford Hill was born into an eminent British family in 1897. His great-great uncle, Sir Rowland Hill, invented the rotary press and introduced the first mail stamp 1840. His father, Sir Leonard Hill, was professor of physiology at the University of London and did seminal work on the cerebral circulation and decompression sickness of divers.

From childhood, Tony, as he came to be called, wanted to be a doctor but the First World War intervened. He volunteered as an aviator for the Royal Navy and was sent to the Greek islands to support the attack on the Dardanelles. His plans were cut short when in November 1917 he was diagnosed with severe pulmonary tuberculosis and was sent home to die. The progress of the disease changed after a therapeutic pneumothorax and he slowly improved. While

recovering he contemplated his career. Medicine seemed to be out of the question and he opted to study economics by correspondence courses from the University of London as he convalesced. Three years later he obtained a Bachelor of Science degree– having attended the university only twice to take examinations.

Early Career

Tony had no desire to make a career in economics. His father's friend, the prominent epidemiologist, Major Greenwood, helped him obtain a grant from the Medical Research Council (MRC) to investigate the reason for the high mortality of young adults in rural Essex. His investigations concluded that the excess was most likely due to selective migration of the fittest to work in urban areas. The success of his research enabled him to obtain further appointments with the MRC and extend his knowledge of statistics by attending courses at the University of London led by Karl Pearson. In 1927 he followed Major Greenwood to the newly-formed London School of Hygiene and Tropical Medicine and taught statistics to at the Postgraduate Medical School at Hammersmith in London (Figure 1).

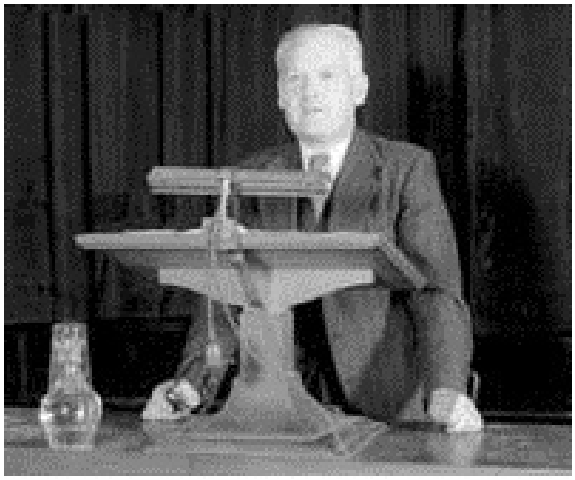

Figure 1. Austin Bradford Hill lecturing.

His lectures were published as a series of 17 popular articles in the Lancet during 1937 and later in book form, *Principles of Medical Statistics* (4). The book became very popular and went through multiple editions making him the best known medical statistician in the world, which is remarkable for someone who held no degree in medicine or statistics. In this book he discussed epidemiological methods for investigating the causes of non-infectious diseases, and introduced randomization. He emphasized the need to compare like with like, to avoid potential sources of bias and to allow for the play of chance. However, he avoided the use of mathematical formulas and set out procedures that needed to be adopted in plain English. By so doing he secured the attention of a medical profession that largely had no basic knowledge of mathematics or

statistics. The book was important in persuading physicians to present their research results both logically and quantitatively.

He wrote of his lectures, "I deliberately left out the words ‘randomisation’ and ‘random sampling numbers’ at that time, because I was trying to persuade doctors to come into controlled trials in the very simplest form and I might have scared them off. I think the concepts of ‘randomisation’ and ‘random sampling numbers’ are slightly odd to the layman, or for that matter, to the lay doctor, when it comes to statistics. I thought it would be better to get the doctors to walk first, before I tried to get them to run. So I had been thinking about controlled trials for all of those 10 years and hoping for an opportunity that might arise” (5).

Landmark Investigations

After the War, Bradford Hill succeeded Greenwood as Professor of Medical Statistics and directed the Statistical Research Unit of the Medical Research Council (MRC). He was particularly influenced by one of Pearson’s students, Ronald Aylmer Fisher, who had pioneered the use of randomization in agricultural experiments. Up until this time medical investigations were usually a before-and-after design, i.e., patients were treated and the results compared to historical controls. He realized that confounding variables so inherent in before-and-after studies could change results. Although Bradford Hill had advocated randomization in his book, he had not been specific about the methods.

In 1946 Bradford Hill was presented with the opportunity to put his theories into practice. He persuaded the MRC to launch randomized controlled trials, one in preventive medicine to test a pertussis (whooping cough) vaccine, the other in clinical medicine to assess the effect of streptomycin in the treatment of pulmonary tuberculosis (6). The latter is generally regarded as the first randomized medical trial with patients randomized to a treatment group and a control group by a process using random sampling numbers and sealed envelopes. These trials were followed by a remarkable stream of articles on the principles of clinical trials including practical and ethical problems.

Meanwhile he launched, with Richard Doll, a case-control study comparing lung cancer patients with matched controls. This study showed conclusively that smoking was the predominant risk factor in developing lung cancer (7). This was followed by other case-control studies, and a long-term prospective study of smoking and health which demonstrated that lung cancer was not the only disease to be caused by smoking. This cohort study was conducted on British doctors, an ideal population whose cooperation was testimony to the respect with which Bradford Hill's work was regarded by his medical colleagues. He was by nature a cautious man, and he had been careful initially to claim that a causal effect of smoking on lung cancer was only one of a number of possible explanations for the association. As the evidence mounted he accepted the causal link as being overwhelmingly the most likely explanation. The reception

was lukewarm and in particular he was disturbed by skeptical remarks from Ronald Fisher. Interestingly, it was Fisher who had nominated Hill as a Fellow of the Royal Society in 1954.

In response to criticism, he formulated 9 principles of causation which were published in 1965 and are listed below (3). Although originally presented as a way of determining the causal link between cigarette smoking and lung cancer, Bradford Hill's Criteria forms the basis of modern epidemiological research. Furthermore these principles are equally applicable to other sciences which study causal relationships between phenomena.

Bradford Hill's Criteria for Causation

1. **Strength.** This is defined by the size of the association as measured by appropriate statistical tests. The stronger the association, the more likely it is that the relation of "A" to "B" is causal. For example, lung cancer death rates are 10-30 times higher in smokers than in nonsmokers.
2. **Consistency.** The association is consistent when results are replicated in studies in different settings using different methods. As an example, Bradford Hill points out that an association between lung cancer and smoking was found in 29 retrospective and 7 prospective studies in 1964.
3. **Specificity.** This is established when a single putative cause produces a specific effect. This is considered by some to be the weakest of all the criteria. Lung cancer attributed to cigarette smoking does not meet this criterion because the death rate of smokers is higher from other causes in addition to lung cancer. When specificity of an association is found, it provides additional support for a causal relationship. However, absence of specificity in no way negates a causal relationship.
4. **Temporality.** Exposure always precedes the outcome. If a factor is believed to cause a disease, then the factor must precede the occurrence of the disease. This is the only absolute criterion. In the case of lung cancer, cigarette smoking invariably occurs before the development of the cancer.
5. **Biological gradient.** By this Bradford Hill means a dose-response relationship. The death rate from lung cancer increases as the number of daily cigarettes smoked increases.
6. **Plausibility.** The association agrees with currently accepted understanding of pathological processes. In 1965, it was known that tobacco tar induced cancer when painted on the skin of mice (8).
7. **Coherence.** The association should be compatible with existing knowledge. Both the incidence of lung cancer and cigarette smoking rose beginning after World War I. In 1964 both the incidence of lung cancer and cigarette smoking were lower in women than in men.
8. **Experiment.** The condition can be prevented or ameliorated by an appropriate experimental regimen. The incidence of lung cancer can be lowered by quitting smoking.

9. **Analogy.** In judging whether a reported association is causal, it is necessary to determine the extent to which researchers have taken other possible explanations into account and have effectively ruled out such alternate explanations. For example, in their investigations Doll and Bradford Hill were careful to match lung cancer patients with controls to eliminate any potential bias related to exposure to occupational or environmental toxins. A questionnaire was designed to identify potential confounding variables including whether cigarette holders and petrol lighters were used, occupation, residence near a gasworks, exposure to different types of home heating, and previous respiratory illnesses and shown to be independently unrelated to lung cancer.

Bradford Hill pointed out that no formal tests of significance could answer the above questions. During his career, he used the simplest mathematical techniques. It is remarkable that as a statistician he relied so little on statistics and he often pointed out that he had no formal training in medicine or statistics. His success was due to a combination of factors but probably most importantly communication of honest experimental and statistical concepts in a way that nearly all could understand.

Hill died in 1991 a few months short of his 94th birthday. Up until the time of his death he continued to collect a 100%, war-related, disability pension from the British Government. In hindsight, his development of tuberculosis may have been a fortuitous occurrence for medical investigation. Despite his disability, he did rather well and should be remembered for his courage in standing up for honest, unbiased research.

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