

Public Health and Medical Humanities History Corner

Austin Bradford Hill: simply the best

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Austin Bradford Hill was born on July 8, 1897, third son of Sir Leonard Erskine Hill, a distinguished medical physiologist, Professor of Physiology at The London Hospital. He grew up in an upper class Victorian family. Sir Leonard, who created an ingenious instrument for blood pressure measuring, had a deep influence on his son. In fact, Bradford decided to follow his father example. He attended Chigwell Grammar School, which was established in 1629, but unfortunately, Bradford's decision to join the Faculty of Medicine coincided with a really big event: First World War. Bradford entered British naval aviation and in 1917 went to the small island of Tenedos, near the coast of Turkey. During a mission he contracted tuberculosis, incurable disease for those times, even if *Mycobacterium tuberculosis hominis* had been identified by Robert Koch in 1885. So, he came back home with a license for an indefinite period and with the compassionate opportunity to die in his own bed at home. Surprisingly, however, his body responded well to available treatments: absolute rest and artificial pneumothorax (introduction of air into the pleural cavity to induce lung collapse). Two years later, he was discharged with a permanent disability pension. His illness prevented him from taking up a career in medicine as he hoped but he used his convalescence to take a degree in economics. Hill's relationships network, however, permitted him to return again on the course left for a force majeure event. In 1923, supported and encouraged by Major Greenwood Hill, a former assistant of his father and a medical officer at the statistical division of the Medical Research Council's (MRC) National Institute

for Medical Research at Hampstead, Hill obtained from MRC a grant to investigate the reasons for high mortality rate of young adults in rural Essex [1]. He collected and analysed data on occupational illnesses, an interest in occupational health that influenced his future career.

Hill built a career in medical statistics at the MRC in Industrial Fatigue Research Board as a statistician. He was enrolled in a part-time course in statistics and statistical analysis at University College, London, led by Karl Pearson. In 1927 Major Greenwood moved to the newly-formed London School of Hygiene and Tropical Medicine (LSHTM) together with his MRC staff. In 1933 Greenwood was appointed Chairman of the University Board of Studies in Hygiene and Academic Professor of Epidemiology and Vital Statistics at LSHTM and invited Bradford Hill to become Reader in Epidemiology and Vital Statistics at the LSHTM.

In 1937 Bradford Hill's lectures were published as a series of articles in *The Lancet* and after that in the book *Principles of Medical Statistics* [2] which has been published in 11 editions during his lifetime. 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" [3].

In 1945 Greenwood went into retirement and gave way to Bradford Hill his chair and intellectual heritage about the importance of statistics in the search for the causes of diseases and the need to design experiments to estimate accurate reliable results, including the effectiveness of therapies. A good opportunity was handily.

The case of streptomycin

In 1946 Bradford Hill entered the Tuberculosis Trials Committee and evaluated the effectiveness of streptomycin against tuberculosis. Streptomycin had been extracted for the first time two years before and in the United States it seemed to be able to eliminate the bacterium responsible for tuberculosis (TB). Again in 1946 another substance able to inhibit *Mycobacterium tuberculosis* growth, with an absolutely new mechanism, was identified. It was the para-aminosalicylic acid (PAS), a chemical compound that can block an essential reaction in the metabolism of the bacteria for its similarity to a substance normally used. Due to its similar but not identical structure, PAS can slow down or even inhibit growth mechanisms. Despite early successes the use of PAS on TB patients, the absolute novelty of the mechanism of action induced skepticism and resistance in the scientific community. Therefore, the Tuberculosis Trials Committee decided to evaluate only streptomycin by a clinical trial. Testing the effectiveness of a treatment by comparing two groups of patients, one who takes the drug and the other that does not take it, was not novelty at those times. From the beginning, however, Bradford Hill fought to utilize an innovative key in the new study on effectiveness of streptomycin: the randomization. Following randomization, the assignment of participants to the intervention (new drug) and to the control group, had to be random. Moreover, randomization introduced an additional point: an order of collocation of subjects that physicians did not know in advance. Random assignment guaranteed absolute impartiality in the construction of the treatment groups with no personal influences by doctors. Randomness became as a synonym for objectivity [4].

So in 1947 first randomized clinical trial started in London to evaluate the

effectiveness of streptomycin and were recruited hundreds of TB patients were, homogeneous in age and medical history. The assignment of patients in the two groups took place according to random numbers personally prepared by Hill and closed in sealed envelopes. In addition, physicians who performed chest radiographs to check the health status of patients were completely unaware about the treatment received by individual participants. After six months, the group of patients treated with streptomycin showed a slight improvement compared to the control group: 4 dead against 14. This was not a great result but Bradford Hill insisted that the study had to be completed and he was right. After three years, mortality rate among patients treated with streptomycin was absolutely comparable with mortality rate of patients treated in the traditional way (rest and artificial pneumothorax): 32 of 55 deaths in the first case, 35 of 52 in the second one. The explanation for this failure is due to the onset of bacterial strains resistant to the antibiotic. The statistical approach of Bradford Hill produced a revolutionary and fundamental effect because it highlighted a limitation of streptomycin therapeutic effect, which would probably escaped in a treatment evaluation only based on clinical observation. If the antibiotic had been used only based on clinical effects observation (as it was then for the majority of drugs), doctors were impressed by his spectacular (but ephemeral) efficacy and would not have noticed the development of resistance. Maybe it would take much longer to realize a study about the death of the patients who at first responded to streptomycin therapy. Based on these results, at the end of 1948 a clinical trial started to evaluate the anti-tubercular action of PAS, a chemical compound until then snubbed as anti-tuberculosis drug. Less than a year after, the Committee announced by a statement that combination of PAS and streptomycin was able to reduce greatly the appearance of resistant strains and could ensure 80% of surviving patients. In 1952, at the end of 3 trials, the final results published in the British Medical Journal [5] indicated that the association of a third drug could lead to survival even at 100% and collateral effects could be limited. Therapeutic effects of this association lasted to the end of the 80's, when new resistant strains appeared with the AIDS epidemic. In the same year, shortly before the publication of these revolutionary findings, tuberculosis killed George Orwell, the author of the novels *1984* and *Animal Farm*, 47 years old. Orwell got sick in 1938 and he was treated in traditional way. Then, after a relapse in 1946, he tried taking streptomycin but, unfortunately, he was allergic and antibiotic therapy should be discontinued. Few years later and his destiny should have been completely different. By that time, randomized controlled trials (RCT) became the standard of reference for the evaluation of new drugs, especially after 1960, when thalidomide tragedy required full adoption of this method. Some doctors criticized this method because they feared the invasion of biomedical research by mathematics, which "reduces patients to stacked numbers and eliminates completely the responsibility of the physician to restore health".

The case of cigarette smoking

Bradford Hill has another fundamental merit: he demonstrated from an epidemiological and statistical point of view the association between cigarette smoking and lung cancer. In the middle of the last century, after two world wars, smokers accounted for nearly all of the male population, regardless of the state of health, so it was not possible to compare smoking and non-smoking. In fact, lung cancer gradually took the place of tuberculosis and victimized mostly among men about 50 or 60 years old. In 1950 victims of lung cancer, for the first time, exceeded those of tuberculosis. In 1947, Bradford Hill, together with Edward Kennaway, Percy Stock and Richard Doll, commissioned by the British Medical Research Council, investigated the possible association between the

increase of death for lung cancer and tobacco use. Hill mostly focused on the evaluation of the dose-effect relationship. So, Hill and other researchers organized a case-control study. It was necessary to take into account other factors including age, sex, place of residence, social class, profession, to minimize possible bias in the data interpretation. A year later, first results from twenty hospitals in London left no doubts: risk of getting sick increases in proportion to the consumption of cigarettes. This correlation was not easy to detect since the rather small numbers at stake without the application of statistics.

These results were confirmed by other studies conducted in different countries, so it was not necessary to repeat the research, published by BMJ in 1950. The impact was huge, because cigarette smoking was well-established habit spreading everywhere, regardless of social class. In 1951 Bradford Hill decided to get further confirmation and drew another study, not retrospective but prospective. The aim was to monitor the causes of death of smokers. The cohort consisted of 60 000 British doctors who received a questionnaire on their smoking habits. To encourage participants to respond, Hill also wrote a letter to the BMJ *Do you smoke?* [6]. In two and a half years he received about 40 000 answers. Data's analysis showed that heavy smokers (more than 25 cigarettes per day) had a 20 times more likely to die of lung cancer. Therefore, there was a direct proportion with the number of cigarettes smoked. A few years later, in 1957, The Lancet published Hill's opinion about this study: a certain proportion of study participants could have been caught in a time when smoked less, perhaps because they were trying to quit. His predictions were confirmed by the time. In 1993, when about half of participants in the study was dead, the final data indicated that lung cancer risk increased even 25 times in heavy smokers.

Dual success of Bradford Hill marked a real paradigm shift in modern medicine: from prevention and treatment of infectious diseases to non-infectious diseases prevention such as cardiovascular diseases or cancer prevention. In addition, there was an unequivocal demonstration of the efficacy of statistical methods to evaluate not only therapeutic interventions, but also the influence of lifestyle and environmental factors on health.

Hill was aware of the possibility of a distorted use of this tool by doctors but he was also convinced that it was the only way to evaluate new treatments and to monitor the effectiveness of those in use yet. In his famous lecture of 1965, *Diseases and the Environment: association or causation?* [7], he described the criteria to design a rigorous clinical study (Table 1).

About consistency he said that it was sufficient to say there was an association between two factors, when the association was verified in at least two independent studies performed at different times and under different experimental conditions. The strength, instead, referred to the concept of relative risk, i.e. the ratio between the proportion of affected individuals in exposed group to presumed cause, and the proportion of affected in non-exposed group. He described the specificity as the consistency with which a certain exposure produced a specific disease, especially for infectious diseases. Each cause must precede its effect: a principle seemingly trivial but decisive for chronic diseases. Finally, the coherence: cause-and-effect interpretation of the data about a disease should not seriously conflict with its natural history and biology but it must be framed in the context of knowledge about the disease.

These simple rules were the application of the fundamental principles of logic. By the simple but rigorous systematization of those rules, Bradford Hill gave a decisive contribution to the growth of epidemiology and he collected the fruits of his genius: in 1950-52 he was President of the Royal Statistical Society, in 1953 he awarded the Gold Medal of the Royal Statistical Society. From 1954 to 1958 he was Member of Council of the Medical Research Council and from 1955 to 1957 he served as Acting Dean, then Dean, of the LSHTM. Bradford Hill later

TABLE 1

HILL'S LIST OF THE CRITERIA FOR CAUSATION

1. **Strength:** A small association does not mean that there is not a causal effect, though the larger the association, the more likely that it is causal.
2. **Consistency:** Consistent findings observed by different persons in different places with different samples strengthens the likelihood of an effect.
3. **Specificity:** Causation is likely if a very specific population at a specific site and disease with no other likely explanation. The more specific an association between a factor and an effect is, the bigger the probability of a causal relationship.
4. **Temporality:** The effect has to occur after the cause (and if there is an expected delay between the cause and expected effect, then the effect must occur after that delay).
5. **Biological gradient:** Greater exposure should generally lead to greater incidence of the effect. However, in some cases, the mere presence of the factor can trigger the effect. In other cases, an inverse proportion is observed: greater exposure leads to lower incidence.
6. **Plausibility:** A plausible mechanism between cause and effect is helpful (but Hill noted that knowledge of the mechanism is limited by current knowledge).
7. **Coherence:** Coherence between epidemiological and laboratory findings increases the likelihood of an effect. However, Hill noted that "... lack of such [laboratory] evidence cannot nullify the epidemiological effect on associations".
8. **Experiment:** "Occasionally it is possible to appeal to experimental evidence".
9. **Analogy:** The effect of similar factors may be considered.

set up a Department of Occupational Health at the LSHTM directed by Richard Schilling. In 1959 he awarded the Galen Medal of the Society of Apothecaries.

He retired in 1961. In 1963 he received an Honorary Degree from the University of Oxford. He became Fellowships of University College London and the London School of Hygiene and Tropical Medicine, Honorary Fellowships of the Royal College of Physicians, the Faculties of Community Medicine and Occupational Medicine, the Royal Society of Medicine, the American Public Health Association, and the Faculty of Medicine at the University of Chile.

In 1968 he awarded an Honorary Degree from the University of Edinburgh.

When he died, on April 18, 1991, Peter Armitage, who succeeded him at the LSHTM, wrote, "to anyone involved in medical statistics, epidemiology or public health, Bradford Hill was quite simply the world's leading medical statistician" [8].

Really a great career. The legacy of Bradford Hill coincides with his attempt to answer the following and simple questions: "Is there any other way to interpret the data that we face? Is there any other explanation likely or more likely than cause-and-effect?". Modern medicine is grateful to Bradford Hill because Hill's attempts have been successful attempts and Hill's answers have been satisfactory answers.

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