Fisher and Bradford Hill: their personal impact

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Fisher

When the time came for me to leave school, there was only one subject I wanted to study: mathematics. I decided, however, for reasons that have been described elsewhere to read medicine instead. It was, therefore, not surprising that, as a medical student, I sought ways in which mathematics could be used in medicine and it was not long before I discovered one, when I came across Fisher’s book on statistical methods for research workers. Most of it was beyond me, but it led me to the $\chi^2$ test, with the result that my first publication was an article in the St Thomas’s Hospital Gazette in which I showed the poverty of the evidence that had been cited by one of my teachers in support of the belief that gonadotropic hormones would help the descent of undescended testes in young boys. For as big or bigger a difference between the descent rate observed in treated boys and that in the historical series with which it had been compared might have been expected to occur by chance six times out of ten. Re-reading the article now, I am struck by the obscurity of the presentation, for I was enamoured of formulae and had not yet had the benefit of Bradford Hill’s teaching of the importance of simplicity of language and the avoidance of formulae when writing for non-statistical readers.

Fisher’s book did not, however, lead me to allocate treatments at random when, after qualification, I had the opportunity for testing medical beliefs and the two trials that I tried to or did undertake during the war relied on alternation to determine treated and control series. One was to test the prophylactic value of sulphonamides as an immediate treatment for wounds. This was turned down by the senior divisional medical officer on the grounds that either such treatment was useful, in which case it should be given to all wounded men, or it was not, in which case I should not waste His Majesty’s money. Unfortunately the senior medical officer could not tell me, in response to my enquiry, whether the treatment was useful or not—that was my province. The other trial, which was never completed owing to a new posting, was to see whether the standard advice to keep patients with infectious hepatitis in bed until the urine was free of bile had any justification.

If, however, Fisher’s book did not lead me to use randomization in a simple trial, it did lead me, many years later, to help design a most economical trial, when Prichard and his colleagues at University College Hospital tested the effect of pronethanol (the first beta-blocker on the market) for the prevention of angina. For a clear benefit was shown ($P < 0.001$) with only 12 patients, two of whom took the drug or a placebo over four periods of a fortnight in each of the six possible orders (ABAB, ABBA, AABB, BABA, BAAB, BBAA).

Bradford Hill

It was Bradford Hill, however, from whom I learnt most. He was sensitive to the value of medical statisticians keeping in touch with clinical medicine. When I went to work with him in 1948 he encouraged me to continue clinical work at the Central Middlesex Hospital under Avery Jones for 2 days a week. I was, therefore, able to put his teaching into practice personally and organized controlled trials of treatments for gastric ulcers with random allocation. It is difficult now, after so many years, to be sure just what one’s motives were at the time. I suspect that I believed that randomization provided the conditions that justified calculation of the probability of obtaining the observed (or more extreme) results by chance and its 95% confidence limits, although randomization obviously had the supreme advantage (if carried out properly) of ensuring the avoidance of selection bias in the allocation of cases. In retrospect, however, it is quite clear that it was the latter advantage that led Bradford Hill to adopt it and to encourage doctors generally to do so as well. This, however, has been adequately stressed by others and I should like to refer here to two other aspects of Hill’s teaching that were of crucial importance to me.

Medical ethics

One was the need to keep ethical considerations constantly in mind when conducting a trial. This was long before ethical committees had been conceived, when the subject was seldom referred to publicly; for it was taken for granted that the essential principles were covered by the Hippocratic Oath that all doctors swore on qualification and the fact that they had taken the oath was deemed to suffice. Hill realized, however, that the conduct of clinical trials raised ethical issues in an acute form—and, indeed, he could hardly do otherwise, as some doctors objected to randomization on what they considered to be ethical grounds—and he devoted much time and thought to the subject. His views were eventually set out in a lecture on medical ethics and controlled trials given at the Royal College of Physicians after he had retired. Hill urged that in many circumstances it might be considered unethical not to conduct a controlled trial and he challenged many of the principles enunciated by the World Medical Association on the grounds that they did not allow for modification to meet the great variety of actual medical problems. His views have been

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discussed in detail by Armitage and it is not his mature conclusions that I want to refer to here, but rather the concern he showed for medical ethics in the design of the first large randomly allocated controlled trial, which so impressed me at the time.

Hill emphasized three points. First, the need to withhold the new streptomycin from some patients with severe pulmonary tuberculosis, despite its striking power \textit{in vitro} and in experimental infection in guinea pigs and the publication of some distinctly promising clinical results, did not constitute an ethical problem. For, to quote Bradford Hill:

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overriding all this evidence in favour of the drug was the fact that at that time exceedingly little of it was available in Great Britain, nor were dollars available for any wide-scale purchase of it from the USA. Except for that situation it would certainly on ethical grounds have been impossible to withhold the drug from desperately ill patients. With that situation, however, it would, the Committee believed, have been unethical not to have seized the opportunity to design a strictly controlled trial which could speedily and effectively reveal the value of the treatment.
\end{quote}

In other circumstances admission to a trial was ethical only if the treating doctor was in genuine doubt about the benefits of the proposed new treatment in comparison with the standard treatment—now codified as the principle of uncertainty. Secondly, if, during the course of the trial, the patient’s condition required some specific treatment he must have it, irrespective of any effect it might have on the comparability of the treatment and control series. The patient’s needs came first; the trial’s requirements came a poor second. Thirdly, common sense should determine the need for a placebo. In theory, it might be desirable to give an apparently comparable treatment in the control group to allow for a psychological reaction. In the streptomycin study, however, this would have required 6-hourly injections of sterile water which would have caused discomfort and this could not be justified when the results of the trial were to be assessed objectively by the survival rate or (in the case of the streptomycin trial) by changes in radiographic appearances read independently without the reader’s knowledge of the patient’s treatment.

\textbf{Conclusion about causality}

The other aspect of his teaching that so impressed me did not affect controlled trials but applied to the interpretation of epidemiological observations. He never to my knowledge discussed whether, in principal, conclusions about causality could be reached by epidemiological observations alone. That was not
his style. What he did was to consider each situation as it presented itself and see where the evidence led.

When, for example, he was asked by the Mond Nickel Company to investigate the possibility of a hazard of cancer at their nickel refinery in South Wales he carried out a cohort study of some 1000 workers and pensioners and came to the firm conclusion that a hazard existed. For, over a period of 10 years (1929–1938), 16 were found to have died from cancer of the lung and 11 from cancer of the nasal sinuses, when about one death might have been anticipated from the former and a fraction of a death from the latter. All other deaths from cancer and from all other causes were about what would have been expected. Subdivision of the population at risk showed that the excesses had fallen wholly on the workers employed in the chemical processes. No similar excesses had been reported elsewhere, no causal agent had been identified, and no animal experimentation had given any support to this wholly statistical evidence. Thus, as he said, ‘we had to make up our minds on a unique event; and there is no difficulty in doing so’.9 that is, that the refining of nickel as carried out in South Wales caused two types of cancer.

My personal experience was in the interpretation of the findings of the case-control study of patients, with or without lung cancer, that Bradford Hill had been asked by the Medical Research Council to conduct to find out the reason for the enormous increase in the mortality attributed to the disease over the previous 30 years. Analysis of the results quickly showed that the characteristic that most clearly distinguished the cases from the controls was the extent to which they smoked, particularly, the extent to which they smoked cigarettes, and we went through in our minds the various possible explanations that could account for it. We were able to dismiss chance and bias and the few factors that we could envisage as causes of confounding and then sought for internal features and external ecological evidence that would support (or negate) the concept of causality. These gave such strong support that we were able to reach the conclusion, without as it happened any firm laboratory experimentation, that ‘cigarette smoking is a cause and an important cause of carcinoma of the bronchus’.10

The various types of evidence that, in sum, enabled this conclusion to be reached were subsequently described in detail in a lecture that Bradford Hill gave 15 years later at the Royal Society of Medicine, entitled ‘The environment and disease: association or causation?’11 and they have subsequently become known as Hill’s guidelines. For they were, he stressed, only guidelines to help in determining causality and not criteria. Only one was sine qua non (namely that exposure to the factor in question should precede the onset of the disease) the rest were aids to thought, but as such they have come to be cited frequently in courts of law when the verdict turns on the causality or not of an observed association.

Conclusion

In this account of some personal reactions to the teaching of two great men I have concentrated on those of Bradford Hill, as I worked closely with him for many years. I do have more recollections of Fisher, including that of a public debate that I had with him at the invitation of Cambridge medical students, but these concern the differences that Hill and I had with Fisher over the interpretation of our findings on smoking and lung cancer and they have been described elsewhere.12 Suffice it to say, in conclusion, that to have known both, even if only superficially in the case of Fisher, was a privilege that I count myself extremely fortunate to have had.

References

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