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Statistical methods in epidemiology: Karl Pearson, Ronald Ross, Major Greenwood and Austin Bradford Hill, 1900–1945

Summary

The tradition of epidemiological study through observation and the use of vital statistics dates back to the 18th century in Britain. At the close of the 19th century, however, a new and more sophisticated statistical approach emerged, from a base in the discipline of mathematics, which was eventually to transform the practice of epidemiology. This paper traces the evolution of that new analytical approach within English epidemiology through the work of four key contributors to its inception and establishment within the wider discipline.

Keywords: Epidemiology – History – Statistics.

"The object of the present *Grammar*", wrote Karl Pearson (1900: 515) towards the end of the second edition of *The grammar of science*, "has been chiefly to show how a want of clear definition has led to the metaphysical obscurities of modern science". Pearson did not explicitly delineate a statistical methodology in his text, but his call for clear definition provoked an enthusiastic response among many young, scientifically-minded men in the last decade of the 19th century, not least in a medical student named Major Greenwood (1880–1947), who had rather have studied either history or mathematics, but whose family tradition had compelled him into medicine (Hogben 1950–51). It has long been recognised among historians of epidemiology that the quantitative methods and statistical philosophy of Karl Pearson (1857–1936) with W. F. R. Weldon (1860–1906), and Francis Galton (1822–1911) generated the processes by which the modern discipline emerged after World War II. The extent of the metaphysical confusion within which the process was generated has generally been underestimated: bacteriology, it is assumed, effectively displaced the existing tradition of epidemiological study, which was only gradually rediscovered in the years after 1910. This perspective overlooks the obduracy of epidemiology, however. Despite the challenge of bacteriology, despite the historicism and metaphysical obscurity re-introduced into the discipline by Charles Creighton, whose monumental *History of epidemics* appeared in the mid-1890s, despite the Pearsonian conviction that every biological event could be reduced to a mathematical formula, epidemiology retained a distinct identity, and consciously maintained and debated that entity, in the years between 1900 and 1940. In that debate, a crucial preparation for the development of the subject after 1945, Major Greenwood played a central part.

Before the 1890s, Victorian epidemiology had been a largely observational, environmentally-oriented science, which employed fairly simple statistical methods. The year 1894 proved something of a watershed, with the publication, on the one hand, of Creighton's History, which sought to illuminate disease causation and behaviour through the examination of past epidemics, and on the other of Emil Roux' successful anti-toxin therapy for diphtheria. The historical approach induced some epidemiological practitioners to go back to older sources, and to develop, from a reading of Hippocrates, Baillou, and especially Sydenham, a more metaphysical approach to problems of disease. The enticing technologies of bacteriology, by contrast, appeared likely to dispense with the need for epidemiology altogether; as one observer noted, once the germ had been found, "The next step is either to exterminate the germ or devise an antidote. This step having been taken, the epidemic disease … is, or ought to be, of only historical interest" (Anonymous 1921). The metaphysical approach developed, no doubt, in part

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as a reaction against epidemiology: those who espoused it tended to be sharp critics both of bacteriology and of the new statistical methods.

For statistics also played a part in this confusing equation. Between the devil of metaphysics and the deep blue sea of bacteriology lay a small band of practitioners who sought the general laws of disease through the application of mathematics, a discipline at once more rigorous and less reductionist than either. Victorian epidemiology had made judicious use of others' expert knowledge – of meteorology, of geology, chemistry, bacteriology, and statistics – but rather as consultant than as integral methodologies. It was, in the tradition of William Farr, a highly pragmatic epidemiology, dealing with the best available data and not straying far from them, using average death-rates, simple methods of statistical induction, and common sense, to draw conclusions – relationships – between illness and insanitary conditions (Greenwood 1935). It was focused largely on local disease outbreaks, on patterns of disease on the ground, and entered into little speculation about issues such as epidemic waves, or the periodicity between outbreaks. Mathematics was not made use of in these investigations, nor were complex statistical analyses: there were few medical men – let alone epidemiologists – with the ability to deal in mathematical issues. Mathematics did not feature in the curriculum of the Victorian medical school, and the only "epidemiological" training then available was vital statistics taught on the Diploma in Public Health courses. Like the great majority of any given population, early twentieth-century medical men shied away from anything at all complex to do with figures.

There were, however, a handful of medical men who were attracted by mathematics as a means of epidemiological analysis, who were interested in trying to establish "natural laws" for the behaviour of disease. The near-universal movement towards new standards of scientific rigour, which had been gathering pace through the 19th century, invited criticism of epidemiology, which, bacteriology apart, contained little that could be described as scientific method. Statistical methods offered an alternative to bacteriology – and a methodology which could be integrated into the existing explanatory models without too evidently relegating the whole discipline to the mathematical practitioners. Indeed, the idea of supplying statistical methods to measure biological variation derived from Francis Galton, whose work influenced the Darwinan zoologist W.F.R. Weldon who, in turn, provided the impetus to Karl Pearson's development of the modern theory of mathematical statistics. Their work represented a new and challenging method of scientific verification and exploration (Magnello 1996). For statistically-minded epidemiologists, the statistical tools which Pearson had created for curve-fitting and goodness of fit tests (for asymmetrical and symmetrical distributions), in addition to the series of correlation methods he devised, had a particular attraction. Having created the Biometric School at University College London (UCL) in 1893, by 1900 Pearson had devised the foundations to the mathematical theory of statistics and the journal *Biometrika* had also been founded by Weldon, Pearson, and Galton. Some three years later, Pearson established the Drapers' Biometric Laboratory at UCL.

It was in the first years of the new century that Greenwood approached Pearson for guidance on using statistics in medical research, so initiating one of two slender contemporary strands of interest in statistical epidemiology. At about this time also the second strand emerged, independently of the biometric stable, in the redoubtable person of Ronald Ross (1857–1932), discoverer of the mosquito transmission theory of malaria. Like Greenwood, Ross was a reluctant medical man, and also like Greenwood, pressurised by his father into the profession. Ross had wanted to be a painter, but he was also multi-talented: painter, musician, physician, and mathematician. Arriving in India in 1881, he spent most of his first six years in the Bengal Medical Service studying mathematics. Writing to G.H.F. Nuttall in 1899, just before he returned home, he asked, "Can you tell me whether immunity has been ever studied mathematically?" A few years later, as external examiner for the Diploma in Tropical Medicine and Hygiene at Cambridge University, he spent his spare time buying maths books in the town (Nuttall 1932–35). Ross had no affiliation with the biometric school, although he appreciated its standing, and sought Pearson's assistance on quantitative matters regarding his work. In 1908, tackling the problem of the relationship between mosquito density and malarial infection in Mauritius, he used a simple difference equation in illustration, later developing applications of the technique in the second edition of his *Prevention of malaria*.

Ross's essay into quantitative epidemiology was closely associated with his interest in malaria. The discovery of the mosquito vector had, inevitably, resulted in unpopular attempts to reduce mosquito numbers as a preventive. It was, however, frequently observed that there was little apparent relationship between numbers of mosquitoes and numbers of malaria victims in a given locality; an observation which was used to argue that the amount of malaria did not depend on the number of mosquitoes, and that as an anti-malarial measure mosquito control was redundant. Experimental investigation being impractical, Ross set himself to examine the question by "a carefully reasoned analysis of the relations between the amount of disease and the various factors which influence it." His first attempt, using the inverse square law, was for Mauritian malaria; in the *Prevention of malaria* he extended his reasoning to the infectious diseases in general with a focus on time-to-time variations. He was subsequently asked to contribute a description of his methods to *Nature* (Ross 1911).

Ross was no proselytiser of quantitative methods in the sense that Greenwood became; with his established reputation as an experimentalist, he did not need to be; he had no career to forge. He was, however, interested in general epidemiological phenomena, and in the business of scientific rigour; indeed David Bradley has noted as one of Ross's major intellectual legacies, "a rational and quantitative approach to communicable disease epidemiology" (Bradley 1997). In his *Nature* article, Ross (1911) claimed to have established three laws of disease behaviour: that the disease (in this case malaria) cannot maintain itself unless the proportion of disease carriers is sufficiently large; that a small increase in carriers above this figure will cause a large increase in the disease; and that the disease will tend to reach a fixed value, depending on the proportion of carriers and the other constants. Ross expressed his doubt that such laws could be achieved except by "such mathematical attempts", and went on to extend their application: the equation showed that yellow fever could "scarcely be considered a disease of men at all", and explained both why certain diseases were absent in the presence of capable carriers, and the phenomenon of smouldering epidemics. He concluded with a generous swipe at existing epidemiological method (Ross 1911):

"These studies require to be developed much further; but they will already be useful if they help to suggest a more precise and quantitative consideration of the numerous factors concerned in epidemics. At present medical ideas regarding these factors are generally so nebulous that almost any statements about them pass muster, and often retard or misdirect important preventive measures for years."

Ross's mathematics were, however, too sophisticated for his wider audience, as Greenwood perhaps perceived, and his methods were only slowly, and at much later dates, taken up by other researchers (Hogben 1950–51). His intervention in favour of quantitative methods in epidemiology was probably important in reinforcing a growing conviction among forward-looking medical institutions that mathematics was a potentially important epidemiological tool. The director of the Lister Institute of Preventive Medicine, Charles Martin, had in 1910 created a post for Major Greenwood as medical statistician; in 1914, the newly-established Medical Research Committee (MCR), funded under the National Insurance Act 1911 to investigate all conditions affecting the health of the people, created a similar post. The latter was filled by John Brownlee (1868–1927), also a Pearsonian disciple. Ross's reputation as a laboratory scientist of international standing lent authority to his endorsement of the mathematical approach: the *British Medical Journal*, for example, noted that his quantitative work was the more important because he was "neither an arm-chair worker nor a 'biometrician' – he was not "obsessed by a vision of the redoubtable Galton Professor of Eugenics", and his advocacy meant that statistical methods had now to be reckoned with seriously as a research technique for "the modern investigator". The journal concluded by quoting Ross directly (Anonymous 1911):

"All epidemiology, concerned as it is with the variation of disease from time to time or from place to place, *must* be considered mathematically, however many variables are implicated, if it is to be considered scientifically at all."

Ross's views on epidemiology, despite his independent stance, strongly echo Francis Galton's dictum that "until the phenomena of any branch of knowledge have been submitted to measurement and number it cannot assume the dignity of a science" (Pearson 1922). For epidemiology, the study on which preventive medicine was based, quantitative methods were essential if it was to have any claim to be a modern science.

The reception accorded to Ross's quantitative studies by the *B.M.J.* make clear the extent to which the association with Karl Pearson was a double-edged sword for those wishing to apply biometric methods to medicine. On the one hand, the methods embodied the new science; on the other, they were irrevocably associated in many educated minds with scientific controversy over issues of heredity. For the preventive medical community in particular, hereditarian attitudes which condemned the past 60 years of public health effort as contributing to the deterioration of the British race, were highly sensitive (Porter 1991). Pearson himself, by his remarks about the deterioration of British intelligence in his Huxley lecture for 1903, had raised hackles among the medical community. Moreover, in 1911–12, Pearson crossed swords with Arthur Newsholme, a leading medical officer and student of epidemiology, over the use of statistics in epidemiological studies. Biometricians with an interest in epidemiology, like Greenwood and John Brownlee (1868–1927) needed to tread warily with the epidemiological and public health community, associated as they were with Pearson, regarded with suspicion by the non-mathematically minded, and medically speaking of parvenu status. As the *B.M.J.* put it in 1911, the modern English school of quantitative methods had "suffered from not numbering among its members any experimental worker of world-wide reputation and perhaps also from the, largely accidental, associations in the public and professional mind between mathematical methods and the heated controversies respecting Mendelism and eugenics" (Anonymous 1911). As Greenwood was repeatedly to record during the inter-war years, in the early 20th century biometrics and statistics were regarded as barely respectable by most medical men. Among the medical statisticians active before World War I, Greenwood, in particular, was consciously fighting a battle to establish medical statistics as a respectable discipline.

The dubious reputation of statistics in epidemiology in the first decade or so of the 20th century was not simply the consequence of widespread mathematical incompetence, or of its association with controversy. Since the 1870s, for example, the vigorous campaign against compulsory infant vaccination against smallpox had compounded suspicions about the use of statistics in medical argument, and these doubts had been reinforced by the fiasco of Almroth Wright's anti-typhoid vaccine in the Boer War. In a discussion of the anti-typhoid vaccine at the Royal Sanitary Institute in 1914, for example, Herbert Snow, an anti-vivisectionist London practitioner, used Wright's vaccine to illustrate his argument that, "there was no note of scientific certainty from beginning to end … the case for inoculation was presented to them now on the strength of statistics. Disease-phenomena being extremely complex, medical statistics were apt to be most unreliable. Every doctor present knew that. At the hands of unscrupulous men they were apt to show all sorts of results. Most medical statistics were not worth the paper they were written on; one could cook them and fake them in any direction".

This general suspicion of statistics, which ran through the medical profession, existed in a more refined form among the established epidemiological community, who operated within the existing field-work tradition. The epidemiologists and public health workers already using statistics, even if in a fairly crude form, were not more receptive to biometric ideas: they feared that more sophisticated methods of analysis would result in a belief that, given sufficiently refined methods of investigation, "truth could be elicited from *any* data, however inaccurate or biased" (Greenwood 1935). Coming from a highly environmentalist, observational, tradition, early twentieth-century epidemiologists were as wary of being over-ridden by statistical methods divorced from biological reality as they were of being subjugated to the minute concerns of the laboratory.

It was against this background of misunderstanding and suspicion that Major Greenwood began to carve out a career for himself as a medical statistician. Unlike John Brownlee, who pursued his interest in statistical epidemiology alongside a career in public health and clinical medicine until his appointment to the MRC, Greenwood early directed his efforts to a specific career in medical statistics. Even before his appointment to the Lister, one of his early publications carried the subscription, "From the London Hospital Statistical Laboratory". In his early 20s, working in Leonard Hill's laboratory at the London, reading the *Grammar of science*, working under Karl Pearson in his Biometric Laboratory, Greenwood began to move towards medical statistics as a career, even though there were no easy openings for a young man with such an ambition. He quickly slanted himself towards epidemiology – the one branch of medicine where statistical methods were already in established use. Although his first publication, in which he acknowledged Pearson's assistance, dealt with the weights of human viscera detailed in the post-mortem records of the London, it already had an epidemiological aspect: it discussed the problems of working with hospital statistics, and concluded by stating that the intention had been to compare the experience of a normal or healthy group with a diseased "group of population" (Greenwood 1904). Greenwood's second paper, with Theodore Thompson of the London Hospital, was on meteorological factors in acute rheumatism; his third on marital infection in respiratory tuberculosis. Although not recorded in the last (1905–06) membership roll of the old Epidemiological Society, he soon appeared as an active member of the Epidemiological Section of the new Royal Society of Medicine, publishing a first paper in the *Proceedings* for 1908. In 1907, he published his first paper in the new, dynamic, Cambridge-based *Journal of Hygiene*, a serial founded (in 1901) and edited by G.F.H. Nuttall, which reflected a distinct strand of epidemiological endeavour: rational, scientific and modern in tone, combining a markedly bacteriological approach with the epidemiological and statistical.

Before the First World War, Greenwood was a vigorous activist and propagandist in his own cause. Well aware of the pervasive medical mistrust of his personal intellectual and professional objectives, he sharpened his wits and his tongue, and acquired, as he later recalled, the "virtues and vices of a minority, a certain courage and a certain trick of over-emphasis [which] always characterise a fighting minority". At this time, he regarded himself primarily as a medical statistician. "I used to see in the statistician the critic of the laboratory worker", he later remarked revealingly, "It is a role which is gratifying to youthful vanity, for it is so easy to cheat oneself into a belief that the critic has some intellectual superiority over the criticised" (Greenwood 1924). Greenwood's contest with Almroth Wright over the viability of the opsonic index in 1908–12 was characteristic of this phase, and was also nicely calculated to attract the attention of the wider medical community (Matthews 1995). It seems likely that Wright's outspoken disdain for traditional preventive medicine and epidemiology, typical of many bacteriologists at that time, added to Greenwood's determination to put the world to rights: the immediate future for any aspiring medical statistician lay – as Greenwood's appointment to the Lister in 1910 was to prove – in precisely those two subdisciplines. Even at this stage in his career, Greenwood was adept at utilising the current pre-occupations of epidemiology to assist his own arguments; with his latent historical sympathies, he quickly took on board the retrospective historical methodology re-introduced by Creighton in the 1890s, and integrated it into his own perspective. At the 17th International Congress on Hygiene, held in London in August 1913, he presented an "exhaustive" account of the history of scarlet fever and of epidemiology in the past 100 years. Discussing the problem of describing the evolution of an epidemic, he argued that in deciding such questions (Anonymous 1913):

"a knowledge of epidemiological history, combined with a firm grasp of the statistical method were as essential parts of the outfit of the investigator in that field as was a grounding in bacteriology. It was … along the lines of Dr Brownlee's work, in applying practically mathematical considerations to the question, that future progress must be looked for …"

In the discussion that followed, Greenwood claimed to be satisfied to find that all the speakers "more or less distinctly recognised" that careful descriptive analysis based on modern statistical methods was an essential part of epidemiology: "the popular impression that such studies have lost their value in the light of bacteriological science seems to be entirely erroneous".

By the eve of the First World War, Greenwood's position in the epidemiological community was established. He had his post at the Lister, he was an active member of the Epidemiological Section of the Royal Society of Medicine, and his list of publications was growing steadily. Political adroitness, and a willingness to take a stand against bacteriology gave him stature within his community, despite the misgivings of his epidemiological colleagues towards biometric methods. Sir William Hamer (1862–1933), a distinguished epidemiologist who worked for the London County Council, was for many years celebrated for having likened epidemiology to the Sleeping Beauty with bacteriologists as authors of the spell. In 1917, he portrayed Greenwood "glowing with epidemiological enthusiasm", in contrast to his own profound depression over the future of the discipline. Talking to Greenwood, he recorded (Hamer 1917):

"For a few brief moments there was revealed over the hills and far away a sunlit world of practical endeavour … I was filled with hope, that, as the good sword of the new statistical methods was in his hand, he might hack a way through and awaken the Princess Epidemiology."

Greenwood's success was in considerable part due to his ability to express himself clearly, and to communicate his statistically-based epidemiology in a variety of literary forms ranging from the immediately accessible to the highly mathematical. His historical sympathies and the fact that he was not a professional mathematician probably helped here: throughout his life he collaborated in his more mathematical-statistical projects with the Cambridge statistician G. Udny Yule (1871–1951). Yule first came into contact with Pearson as an engineering student attending Pearson's lectures on applied mathematics and mechanics in the late 1880s, and later became a Demonstrator in Pearson's Biometric Laboratory. Yule's contributions to the modern theory of mathematical statistics include his introduction of least squares measures as a means of interpreting multiple regression (which has since remained an important tool for regression). His work on statistical measures of association in 1899 engendered further statistical developments for Pearson, who devised a series of methods to measure statistical associations and correlations for discrete variables between 1899 and 1909. Unlike John Brownlee, whose papers were so reliant on mathematical-statistics that only those trained in the Biometric School could read them, Greenwood took considerable pains to keep a significant proportion of his work in language comprehensible to ordinary educated people. He admired Yule for his ability to express difficult mathematical arguments in language accessible to attentive readers, and he acknowledged that Brownlee's "not very attractive" literary style might deter readers from his work. While Greenwood could, and did, produce rigorous mathematical-statistical papers on epidemiology, he was entirely capable, as his *Epidemics and crowd diseases* demonstrates, of writing with perfect clarity for the ordinary educated reader.

As for so many of his generation, Greenwood's perspective on his life's-work was altered by his experiences in the First World War. Although he did not see active service, having become a sanitary officer in the Royal Army Medical Corps before being seconded to the Ministry of Health and Welfare for statistical work, Greenwood came to see the war as a melting-pot for academic research and its personnel: "The events of the great war", he noted in 1919, "have led to the co-operation of isolated investigators now…". (Greenwood 1919).

Of even greater significance for his personal perspective, experience of the terrible influenza epidemic of 1918–19 forced a re-evaluation of the value of statistical methods: from this time onwards, the identity of Greenwood the medical statistician blurred imperceptibly into that of Greenwood the epidemiologist, as he realised that neither statistical techniques nor laboratory investigation could satisfactorily describe disease behaviour, that what was needed was to "learn more of the grammar of the language of epidemiology" (Greenwood 1932).

The years 1919–20 also brought fresh professional associations. He was appointed to the new Ministry of Health as medical officer in charge of statistical work, and acquired new involvements with the National Institute for Medical Research and the Medical Research Council, in whose Hampstead premises he had his office. In 1920, moreover, he began his association with W.W.C. Topley (1880–1942), whose own wartime experience of the Serbian typhus epidemic of 1914–15 had turned him from a straightforward minute pathologist into an experimental epidemiologist, pursuing the laws of epidemic behaviour among populations of laboratory animals. For both Greenwood and Topley, first hand experience of major epidemics resulting from mass population movements occasioned by war were critical in shaping their post-war research concerns. For nearly 20 years, from circa 1920 to the outbreak of World War II in 1939, the two collaborated in an extraordinary enterprise of experimental epidemiology, with Topley designing the laboratory experiments and Greenwood and his statistical protegés providing the analytical expertise.

A continuing theme of Greenwood's reflections on the relationship between epidemiology and statistics, and one reason why he found experimental epidemiology so attractive, was the difficulty of balancing mathematical-statistical constructions against biological events. This problem was also, of course, that at the crux of general medical scepticism of the value of statistics and was, in the 1930s, to pre-occupy Greenwood's protegé and later successor, Austin Bradford Hill, as he began to drive statistical methods into clinical practice. Both Greenwood and Brownlee had, for example, been attracted by Pearson's family of frequency curves, which was capable of describing effectively both asymmetrical and symmetrical distributions (which included the normal curve), so enabling statisticians to deal with a wide range of frequency systems. According to Greenwood, Brownlee took this work further than any other contemporary epidemiologist, with the objects of first graduating the statistics, and then, if possible, of classifying epidemics on the basis of the type of curve found. The results were fairly satisfactory as far as graduation was concerned, but he found it impossible to obtain any useful classification. The only clear result was that Pearson's Type IV curve (the Family of Asymmetric Curves) was found more commonly than any other. As Greenwood remarked, "The more fundamental problem of epidemiology, viz., that of discovering the laws of which the epidemic, whether viewed in its temporal or spatial relations, is an expression, could scarcely be solved in this way". By using Pearson's method of curve-fitting, Brownlee eventually obtained a curve which effectively described certain symmetrical epidemics, but he could not obtain any function which accounted satisfactorily for the marked asymmetry characteristic of many epidemics. Ross's theory of happenings, which similarly attempted a mathematical law of epidemics with an *a priori* method, was not vastly more successful in Greenwood's view, even though he considered that Ross had achieved important results in the genesis of an asymmetrical curve with general application. "It is too early", he cautioned, "to speak with confidence". Once restrictions were relaxed, he warned, the analysis would inevitably become more intricate and, "having devised an *a priori* law, one must devise, usually by [Pearson's] method of moments, a way of applying the law to statistical data" (Greenwood 1916). Thus, Greenwood also emphasised the utility of Pearson's family of curves for fitting empirical distributions to one of Pearson's theoretical distributions. Greenwood was one of the few epidemiologists capable of understanding Ross's calculations at this time; it has been suggested that he found Ross's methodology too theoretical to be practicable as a way forward for contemporary epidemiology (Hogben 1950–51).

The use of mathematical-statistics for medical data concerned Greenwood in another, more practical, way at this time. In the early months of the war, Greenwood and Yule were engaged in a fairly comprehensive investigation of the inoculation statistics of cholera and typhoid, which led them into a consideration of the theoretical problems associated with their interpretation. As part of this inquiry, they used firstly Pearson's chi-square goodness of fit test (of 1900) to determine how well an observed distribution compared to the theoretical distribution. They chose this test because it provided a criterion to determine if the probability that any difference between the incidence- or fatality-rates of the inoculated and uninoculated were statistically significant. They found that those who were inoculated recovered from typhoid and thus there was a lower mortality rate in these patients. They argued that the "case in favour of anti-typhoid inoculation as a practical means is very strong" (Greenwood & Yule 1914–15). They wanted to determine next the ratio of "advantage of immunisation process as the difference between fatality rates" using data from cholera. They used the tetrachoric correlation coefficient and found mainly moderate correlations (ranging from 0.35 to 0.53) with one high correlation (0.83). In the final section of the paper, they wanted to know whether the cholera or the typhoid inoculations produced better immunisation results. To examine their data they used Pearson's product-moment correlation (which was very similar to Pearson's tetrachoric correlation coefficient) to determine if there was a statistically significant difference between the results from typhoid and cholera. The results in the final section were disappointing as they could not determine which set of inoculations was more efficacious. "The general lesson to be learned", they concluded, "is that mathematical difficulties of method must not absorb the whole energies of the statistician". Pearson and his pupils had provided a solution for many mathematical difficulties, but "Dr Brownlee and Dr Maynard alone, so far as we are aware, have assigned a due measure of importance to the biological difficulties of interpretation which present themselves in connection with such inquiries".

By 1916, therefore, Greenwood was already moving into a position from which he viewed the efficacy of mathematical statistics, as applied both to epidemiological theory and to laboratory medicine, with some reservations, as being too detached from the biological reality of disease behaviour. His experience of the terrible influenza epidemic of 1918–19 compounded these doubts, as he tried to make sense of the raw data of the outbreak. Looking back to that event in his Herter Lectures of 1931, Greenwood recalled,

"I [had] thought that with the sharp tools of statistical research Pearson had forged and a certain emotional faith in eugenics, we should reach epidemiological truth. Confronted with a mass of data, good, indifferent, bad, which the great epidemic of 1918–19 provided, upon which it was my duty to report, I realised my ignorance and helplessness."

That helplessness, in his first year as the first official Government statistical expert, must have been somewhat traumatic, forcing a re-evaluation of his professional stance. In a paper delivered in 1924 at the Institute of Pathology and Research at St Mary's Hospital, on Almroth Wright's home ground, he noted, "In some ways I value [the statistical method] more, in others less, than I did as a youth" (Greenwood 1924). Although, he continued, he had not yet reached the point where he thought statistical criticism of laboratory investigations useless (as did, for example, Almroth Wright), he now placed "enormously more" value on direct collaboration, on the making of statistical experiments, and on the "permeation of statistical research with the experimental spirit". His collaboration with Topley furnished one of the many examples of the virtue of using life tables for epidemiological problems: the life tables and "shop-arithmetic" of William Farr were all that had been applied to the data of Topley's controlled mouse populations. By these means, however, "it is almost certain, that we shall reach a clearer insight into the phenomena of epidemic disease than generations of unintegrated experimental and statistical work have achieved; armed with that knowledge, we may be able to interpret the record, both minute and defective, of human history" (Greenwood 1924).

Although Greenwood emphasised the importance of statistics to his St Mary's audience, he also stressed that different diseases might call for different investigative methods. Treading carefully, in a political situation of some delicacy, he noted the potential value of the element of heredity as an explanatory factor in the causation of some diseases. "Even the most convinced adherents of the environmental as opposed to the genetic origin of ill health", he now wrote, would hardly deny that Pearson's investigations of the factors influencing the ill-being or well-being of children had given a clearer insight into the roles of different possible and probable causes of ill-health. "Nature *does* present us with skeins not to be unravelled by the most habile experimenter, cases where the A, the B, and C *cannot* be studied in isolation". In such cases, the calculus of correlations was an invaluable tool (Greenwood 1924).

The inter-war years saw Greenwood persistently working over the problematic relationships of biology, statistical method and natural law. In a well-established, if perhaps increasingly old-fashioned, scientific tradition, he seems still to have been pre-occupied with the possibility of establishing natural laws of disease behaviour if only a correctly balanced biological/statistical accommodation could be achieved. In this sense, he was neither an original nor a creative epidemiologist – as both he and others noted, his long-term contribution to the subject was rather in the careers he fostered, in the department he established at the London School of Hygiene and Tropical Medicine (LSHTM) after 1927, in the scientific profile he maintained for epidemiology. While he continued to enjoy his work with Topley, and counted it as his most important research achievement, he did not take his discipline forward methodologically in these years. He worked with existing statistical tools, he did not modify, refine or develop them significantly. Summing up the state of the discipline in 1935, he could only remark: "There is no real doubt that the present standard of descriptive accuracy is far higher, and the analysis to which the data are subjected are less superficial, then even twenty-five years ago" (Greenwood 1935). Despite the enormous quantities of data provided in the past century by death registration and disease notification, despite the "hecatombs of animals" offered on the altars of experimental science, the new discipline of mathematical statistics had not succeeded in resolving the questions which had exercised epidemiologists for generations: the problems of secular variation, of changes of type, of methods of spread. Epidemiologists in the 1930s could not even explain why death-rates from tuberculosis had fallen, or why the virulence of scarlet fever had diminished.

Greenwood's central preoccupation here was the problem of elucidating the fundamental laws of disease – the epidemiologists' holy grail. He thought that the available series of disease-data were not long enough by comparison with the infinitely longer history of human populations to be of use; but that there was already so much medico-statistical information that choices for analysis had to be made, and even a choice involved so many further variables that the available statistical tools were not sophisticated enough to achieve satisfactory analyses. The central problems of epidemiology in searching for fundamental laws were, he considered, imperfect statistical methods and the range of significant factors in disease causation (Greenwood 1935):

"The statistician, however mathematical, has no magic spell which frees Dame Nature to treat him differently from other men. She always answers truthfully the question you ask her, not the question you *meant* to ask but the one you *did* ask."

Although the lectures from which these ideas were drawn were for public health men, and designed to generate a general interest in epidemiology rather than to stimulate innovative epidemiological research, Greenwood's reflections do indicate the limitations of his own brand of epidemiology. To free up epidemiological inquiry, techniques to account much more precisely for unknown or obscure variables, and more sophisticated methods which would allow equations involving the further powers of variable, had to be evolved. *Epidemics and crowd diseases*, although not a specialist textbook, still reveals the limitations of English epidemiology as represented by Greenwood on the eve of World War II. Although in terms of statistics and experiment, epidemiology had extended its perspectives since the Victorian period, the book was in many respects recognisably in the same tradition, emphasising the observation of biological events, stressing the importance of collaboration between different specialist workers, insisting that statistical methods should not play a dominant role. "I am a statistician by training," Greenwood had observed in 1931, "I emphasise the statistical aspects … I do not wish to suggest that they are therefore the most important" (Greenwood 1932).

Within Greenwood's department at the LSHTM, however, a revolution – it is fair to call it that, although it also had roots in the United States – was brewing. Austin Bradford Hill (1897–1991), son of the physiologist Leonard Hill, who had fostered Greenwood's own research career, had been one of Greenwood's earliest protegés. Debarred from a career in medicine by tuberculosis and the loss of a lung, Hill had studied economics at Greenwood's suggestion in the aftermath of World War I. After qualifying in economics at the University of London in 1922, Hill found a place in the Medical Research Council's Statistical Unit managed by Greenwood. Under Greenwood, the Unit became closely associated with the new department of epidemiology and vital statistics at the LSHTM after 1927, and in 1933 Hill was promoted to a Readership at the School. He was to succeed Greenwood as Professor in 1945, and to assume the directorship of the Statistical Unit.

Hill's early research career was unremarkable. He had begun by intending to pursue a career in epidemiology with a special interest in occupational medicine. Greenwood, too, had developed an interest in this subject during the first war, and before the second war Hill was largely occupied in collecting and analysing data relating to occupational illness – of London bus drivers, printers, cotton weavers and spinners, and asbestos workers; he was also involved in the Topley and Greenwood experimental epidemiology project. These surveys, as Richard Doll later observed, were characteristic of their period, using routinely collected morbidity and mortality data, and attempting to elucidate them by means of population surveys. The originality of Hill's approach to epidemiology, and his stature as a creative epidemiologist, only began to become apparent after the second war, when he had succeeded Greenwood as professor. His development of the traditional survey methods, of the methods of case-control and cohort studies, and his guidelines for drawing conclusions about causal relationships, were all part of a wider upsurge of creative energy in the discipline of epidemiology which distinguished the post-World War II period (Susser 1985). None the less, much of the creative thought and planning behind some of the later innovations took place before the War.

Bradford Hill's introduction of randomisation into the clinical arena, his development of the modern randomised clinical trial, and the prospective case-control study on smoking and lung cancer completed with Richard Doll, have tended to overshadow his other contributions. However, the "trial run" of randomisation took place in the epidemiological field, before the advent of streptomycin provided the opportunity of extending the technique into clinical medicine. Mervyn Susser (1985) has designated the prophylactic trials of vaccines as epidemiologists' "own firm ground". It is a designation which Bradford Hill did much to make possible. In Britain in particular, a century-long tradition of opposition to immunisations laid every vaccine introduced up to 1940 and beyond open to both lay and medical suspicion and condemnation, and in the course of this long-standing argument statistical assessments of efficacy had come to be viewed with particular mistrust. This was not a uniquely British phenomenon, but the British were perhaps the most extreme among the European peoples in their cautious reaction to vaccines. The inter-war years had, however, seen an acceleration of research in immunology, with vaccines for tuberculosis, diphtheria and whooping cough being actively developed and tried. While both the tuberculosis and diphtheria vaccines had their problematic aspects, whooping cough vaccines proved significantly more difficult to manage in the developmental stages. The impetus for developing a satisfactory vaccine was strong, for the disease was still a notable killer of infants and young children, besides being a most distressing illness for both victim and attendants. Hill's interest in whooping cough dated from at least the early 1930s, when his first disease-specific publication dealt with the disease (Hill 1933). When in 1942 the MRC broached their intention of trying out whooping cough vaccines with a view to extended preventive action against the disease, Hill took the opportunity of introducing the randomisation feature into these large-scale trials.

Hill's originality lay, of course, in his application of statistical randomisation to preventive medicine, and in his successful promulgation of Pearsonian statistics for medical research and specifically for clinical trials. Hill was, however, somewhat in contrast to Greenwood, basically interested in medicine rather than in history or statistics; he intended from the start of his career to be an epidemiologist, and he would have preferred to be remembered as an epidemiologist rather than as a statistician. Before 1940, it is possible to examine developments in British epidemiology to a great extent in isolation from developments in European and American epidemiology, as has been done in this essay. Greenwood, of course, had his contacts with American epidemiologists and biometricians – and in particular was a close friend of Raymond Pearl (who had his training in Pearson's Biometric Laboratory) – but as an academic discipline, epidemiology was a newly emerging one, and did not solidify its institutional structures and objectives in research and training until the 1940s in either England or America. When he succeeded Greenwood at the London School in 1945, Hill rapidly created a department of young research workers whose statistical and epidemiological expertise far outstripped anything in Greenwood's pre-war department. As Mervyn Susser (1985) has remarked, the Second World War marks a "convenient watershed" in the history of epidemiology, on which can be hung the transition from pre-occupation with infectious diseases to a recognition that chronic diseases and a range of other biomedical problems are important in the compass of the discipline. It also marks the definitive transition from an empirical to a statistical methodology. Significantly, Hill renamed his LSHTM department "Medical Statistics and Epidemiology". This change of emphasis may not have been fully approved by Major Greenwood. As early as 1924 he had envisaged the possibility that at some future date, "a brilliant young mathematician, building on higher foundations laid by Karl Pearson, will assert that in medical, or in any other biological research, the judgement of the biometrician must be final; he must be the ultimate court of appeal". It was not a prospect which appealed to Greenwood. Summoning, with some irony, the shade of the old adversary who so vehemently objected to the imposing of statistical discipline on medical judgement, he noted that when that time came, "I shall be found enlisted under the banner of Sir Almroth Wright … the statistician must be the equal not the predominant partner" (Greenwood 1924).

Zusammenfassung

Statistische Methoden in der Epidemiologie: Karl Pearson, Ronald Ross, Major Greenwood und Austin Bradford Hill, 1900–1945

Die Tradition der beobachtenden epidemiologischen Studien und die Verwendung der Bevölkerungsstatistik geht ins 18. Jahrhundert in Grossbritannien zurück. Zu Beginn des 20. Jahrhunderts setzte sich jedoch ein neuer und anspruchsvollerer statistischer Ansatz durch, der seine Basis in der mathematischen Disziplin hat und letztendlich die epidemiologische Praxis veränderte. Der vorliegende Artikel befasst sich mit der Entwicklung dieser neuen analytischen Methode in der englischen Epidemiologie. Dies geschieht anhand der Arbeit von vier Männern, die ganz wesentlich zur Einführung und Anerkennung dieser Methode innerhalb der weiter gefassten Disziplin beigetragen haben.

Résumé

Méthodes statistiques en épidémiologie: Karl Pearson, Ronald Ross, Major Greenwood et Austin Bradford Hill, 1900–1945

La tradition des études épidémiologiques basées sur l'observation et sur l'utilisation des statistiques sanitaires remonte en Angleterre, au 18e siècle. A l'orée du 20e siècle, cependant, une approche statistique nouvelle et plus sophistiquée est apparue, reposant sur les mathématiques, qui va transformer la pratique de l'épidémiologie. Cet article retrace l'évolution de cette nouvelle approche analytique au sein de l'épidémiologie anglaise à travers les travaux de quatre personnes qui ont contribué à son élaboration et à son établissement en tant que discipline plus large.

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