CHAPTER 1

HISTORY OF STATISTICAL THINKING IN MEDICINE

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1. Introduction

Biostatistics is a very hot discipline today. Biostatisticians are in demand in the United States. Medical researchers appreciate statistical thinking and applications. In laboratory science, clinical research and epidemiological investigation, statisticians' collaborations are sought after. In many medical journals, statisticians are asked to serve as reviewers. In NIH (National Institutes of Health) grant applications, statisticians are required to be collaborators and statistical considerations have to be incorporated. In pharmaceutical development, drug companies recruit statisticians to guide study design, to analyze data, and to prepare reports for submission to FDA (Food and Drug Administration). All in all, statistical thinking permeates medical research and health policy. But it was not this way in the beginning. This article describes the history of application of statistical thinking in the medicine.

2. Laplace and His Vision

Near the time of American independence and the French Revolution, French mathematician Pierre-Simon Laplace (1749–1827) worked on probability theory. He published many papers on different aspects of mathematical probability including theoretical issues and applications to demography and vital statistics. He was convinced that probability theory could be applied to the entire system of human knowledge, because the principal means of finding truth were based on probabilities. Viewing medical therapy as a domain for application of probability, he said that the preferred method of

treatment would manifest itself increasingly in the measure as the number of observations was increased.[1,2]

Laplace's view that the summary of therapeutic successes and failures from a group of patients could guide the future therapy was hotly debated within the medical community. Many famous physicians like Pieere-Jean-Georges Cabanis (1757–1808) claimed that the specificity of each patient demanded a kind of informed-professional judgment rather than guidance from quantitative analysis. According to their view, the proper professional behavior for physicians in diagnosing and treating disease was to match the special characteristics of each patient with the knowledge acquired through the course of medical practice. Physicians were able to judge individual cases in all of their uniqueness, rather than on the basis of quantitative knowledge. Cabanis rejected quantitative reasoning as an intellectual distraction and viewed medicine as an "art" rather than as a "science."[3]

On the other hand, other prominent physicians like Philippe Pinel (1745–1826) said that physicians could determine the effectiveness of various therapies by counting the number of times a treatment produced a favorable response. He considered a treatment effective if it had a high success rate. He even claimed that medical therapy could achieve the status of a true science if it applied the calculus of probabilities. His understanding of this calculation, however, was restricted to counting; he did not understand the detailed nature of the probability theory being developed by Laplace.[4]

3. Louis and Numerical Method

Later another prominent clinician, Pierre-Charles-Alexandre Louis (1787–1872), considered that enumeration was synonymous with scientific reasoning. He followed Laplace's proposal that analytical methods derived from probability theory help to reach a good judgment and to avoid confusing illusions. His method consisted of careful observation, systematic record keeping, rigorous analysis of multiple cases, cautious generalizations, verification through autopsies, and therapy based on the curative power of nature. He said that the introduction of statistics into diagnosis and therapy would ensure that all medical practitioners arrive at identical results.[5]

In his study of typhoid fever, which collected patient data between 1822 and 1827, Louis observed the age difference between the groups who died (50 patients with mean age 23) and who survived (88 patients with mean

age 21). He also compared the length of residency in Paris and concluded that the group which survived lived in Paris longer. More importantly, Louis studied the efficacy of bloodletting as a therapy for typhoid fever. Among the 52 fatal cases, 39 patients (75%) had been bled. The mean survival time for the bled cases was 25.5 days contrasted to 28 days for those who were not bled. Of the 88 recovery cases, 62 patients (70%) were bled, with the mean duration of disease being 32 days as opposed to only 31 days for those not bled.[6]

Louis also studied the efficacy of bloodletting in treating pneumonitis and angina tonsillaris, and found it not useful. At that time, the method of venesection was defended by Francois Joseph Victor Broussais (1772–1838), the chief physician at the Parisian military hospital and medical school. Broussais claimed that diseases could be identified by observing the lesions of organs. Then patients could be treated by bleeding the diseased organ and by low fat, since most diseases were the result of inflammation. Louis, in contrast with Broussais, emphasized quantitative results from a population of sick individuals rather than using pathological anatomy to observe disease in a particular patient. He contended that the difference between numerical results and words, such as "more or less" and "rarely or frequently," was "the difference of truth and error; of a thing clear and truly scientific on the one hand, and of something vague and worthless on the other." He also proposed the basic concept of controlled clinical trial.[7]

Louis's work created more debates before the Parisian Academies of Sciences and Medicine in the late 1830s. The triggering issue was the question of the proper surgical procedure for removing bladder stones. A new bloodless method for removing bladder stones (lithotrity) was investigated by the surgeon and urologist Jean Civiale (1792–1867). He argued that, given the fallacy of human memory, surgeons tend to remember their successful cases more than their unsuccessful ones; errors result from inexact records. He published the relative rates of death from the traditional surgical procedure and the lithotrity. The death rate of the old procedure was 21.6% (1,237/5,715); the death rate for lithotrity was 2.3% (6/257).[3]

In response to Civiale's statistical results, the Academy of Sciences established a commission in 1835 including the mathematician Simeon-Denis Poisson (1781–1840) and the physician Francois Double (1776–1842). Rejecting the attempt to turn the clinician into a scientist through the statistical method, Double believed that the physician's proper concern should remain the individual patient. He claimed it was inappropriate to elevate

the human spirit to that mathematical certainty found only in astronomy; the eminently proper method in the progress of medicine was logical not numerical analysis.[8]

During that time, Lambert Adolphe Jacques Quetelet (1796–1874) proposed a new concept of the "average man," defined as the average of all human attributes in a country. It would serve as a "type" of the nation similar to the idea of a center of gravity in physics. He formulated this idea by combining his training in astronomy and mathematics with a passion for social statistics. He analyzed the first census of Belgium (1829) and was instrumental in the formation of the Royal Statistical Society. He maintained that the concept of statistical norms could be useful to medical practice as it had been to medical research.[9] At the same time, Poisson applied probability theory to the voting patterns of judicial tribunals. He used the "law of large numbers" to devise a 99.5% confidence interval for binomial probability.[10]

In 1837, in a lecture delivered before the French Academy of Medicine, physician Risueno d'Amador (1802–1849) used the example of maritime insurance to illustrate why the probability was not applicable to medicine. If 100 vessels perish for every 1,000 that set sail, one still could not know which particular ships would be destroyed. It depended on other prognostic variables such as the age of the vessel, the experience of the captain, or the condition of the weather and the seas. Statistics could not predict the outcome of particular patients because of the uniqueness of each individual involved. For d'Amador, the results of observation in medicine were often more variable than in other sciences like astronomy.[11]

In the ensuing debates, Double commented that a Queteletian average man would reduce the physician to "a shoemaker who after having measured the feet of a thousand persisted in fitting everyone on the basis of the imaginary model." He also claimed that Poisson's attempts to mathematize human decision-making were useless because of the pressing and immediate concerns of medical practice.

Louis-Denis-Jules Gavarret (1809–1890), trained in both engineering and medicine, addressed the criticism of d'Amador in 1840. He maintained that the probability theory merely expressed the statistical results of inductive reasoning in a more formal and exact manner. He emphasized that statistical results were useful only if certain conditions prevailed — namely, the cases must be similar or comparable, and there must be large enough observations. He followed Poisson's example in requiring a precision of 99.5% or 212:1. He commented on the insufficient sample size in Louis' study of typhoid fever.[12]

In responding to the work of Gavarret, Elisha Bartlett (1804–1855), a professor of medicine at the University of Maryland and a student of Louis, said that the value of the numerical method was exhibited by Louis, and its true principles were developed and demonstrated by Gavarret.[13] However, the British statistician William Augustus Guy (1810–1885) in his Croonian lecture before the Royal College of Physicians in 1860, said that Gavarret's confidence interval could only be applied in rare occasions, and the results obtained from averaging a small number of cases could generally be assumed to be accurate.[14] In Germany, an ophthalmologist Julius Hirschberg (1843–1925), concerning about the number of observations required by Gavarret's assumption of 212:1 odds, he modified the formula by using a lower standard of confidence of 11:1 or 91.6%.[15]

4. Statistical Analysis Versus Laboratory Investigation

In articles published in 1878 and 1881, German physician Friedrich Martius (1850–1923) commented that the dreams of Louis and Gavarret about a new era of scientific medicine had not been fulfilled due to the general "mathematical unfitness" of the medical profession as a whole. As one trained in laboratory methods, he said that the basis for science lay in laboratory experimentation rather than mere observation and the collection of numerical data.[3]

The legacy of Louis was in his claim that the clinical physician should aspire to become a scientist. But after Louis's retirement from the medical scene by the mid 1850s, some medical researchers began to argue that the compilation of numerical results might provide some useful insights about therapy; however, these results should not posses the authoritative status as "science." Friedrich Oesterlen (1812–1877) said that "scientific" results should be the discovery of knowledge which determined the causal connections, not just the discovery of the correlation.[16]

When Joseph Lister (1827–1912) published his pioneering work with antiseptic surgery in 1870, he noted that the average mortality rate was 45.7% (16/35) for all surgical procedures performed at the University of Edinburgh in the years 1864–1866 (before antiseptic methods were introduced). And it was 15% (6/40) for all surgical procedures performed in the three-year period 1867–1869 (after the introduction of antiseptic methods). Although he used this statistical result to show the efficacy of the new antiseptic method, he claimed that the science behind this was the germ theory of disease as proposed by Louis Pasteur (1822–1895).[17] Pasteur developed the

germ theory and the concept of immunity. He carried out a clinical trial in 1881 to test his new vaccine against anthrax.

The founder of 19th century scientific positivism, Auguste Comte (1798–1857), believed that mere empiricism (as practiced by Louis) was not really useful for medicine.[18] Claude Bernard (1813–1878) proposed that the science of medicine resided in experimental physiology, rather than observational statistics. As a result of his laboratory-based orientation, he claimed that the experimental investigation of each individual patient could provide an "objective" scientific result. He agreed with Louis's vision of medicine as a science but saw the science of medicine as focused on the physiological measurements of individual patients.[19]

Other prominent clinicians at that time, like German Carl Wunderlich (1815–1877), tried to steer a middle ground between Louis and Bernard and synthesized both approaches. They collected a mass of quantifiable physiological data and tried to analyze it using numerical method. However, this approach was not accepted by the medical community in general, and many still opposed the process of quantification and remained focused on the individual patient.[20]

5. The Beginning of Modern Statistics

The founders of the Statistical Society in London in 1834 chose the motto "Let others thrash it out," thus set the general aim of statistics as data collection. Near the end of the 19th century, scientists began to collect large amounts of data in the biological world. Now they faced obstacles because their data had so much variation. Biological systems were so complex that a particular outcome had many causal factors. There was already a body of probability theory, but it was only mathematics. Prevailing scientific wisdom said that probability theory and actual data were separate entities and should not be mixed. Due to the work of the British biometrical school associated with Sir Francis Galton (1822–1911) and Karl Pearson (1857–1936), this attitude was changed, and statistics was transformed from an empirical social science into a mathematical applied science.

Galton, a half-cousin of Charles Darwin (1809–1882), studied medicine at Cambridge, explored Africa during the period 1850–1852, and received the gold medal from the Royal Geographical Society in 1853 in recognition of his achievement. After reading Charles Darwin's 1859 work *On the Origin of Species*, Galton turned to study heredity and developed a new vision for the role of science in society.[21] The late Victorian intellectual movement of

scientific naturalism gave rise to the belief that scientifically trained persons must become leaders of British intellectual culture.

Galton accepted the evolutionary doctrine that the condition of the human species could be improved most effectively through a scientifically directed process of controlled breeding. His interest in eugenics led him to the method of correlation. He applied the Gaussian law of error to the intelligence of human beings and, unlike Quetelet, was more interested in the distribution and deviations from the mean than in the average value itself.

As a disciple of Galton, Karl Pearson, the founding father of modern statistics, created the statistical methodology and sold it to the world. Pearson changed statistics from a descriptive to an inferential discipline. He majored in mathematics at King's College, Cambridge. After Cambridge, he studied German literature, read law and was admitted to bar. He became professor of mathematics at King's College, London in 1881 and at University College, London in 1883. In June 1884 at age 27 he was appointed to Goldsmid Professor of Applied Mathematics at University College, London. Biologists at that time were interested in genetics, inheritance, and eugenics. In 1892 Pearson began to collaborate with zoologist WFR Weldon, Jodrell Chair of biology at University College, and developed a methodology for the exploration of life. Two years later Pearson offered his first advanced course in statistical theory, making University College the sole place for instruction of modern statistical methods before the 1920s.[22]

Following Galton, Pearson maintained that empirically determined "facts" obtained by the methods of science were the sole arbiters of truth. He argued for the almost universal application of statistical method, that mathematics could be applied to biological problems and that analysis of statistical data could answer many questions about the life of plants, animals, and men.[23] After a paper was rejected by the Royal Society, he together with Galton and Weldon founded the journal *Biometrika* in 1901 to provide an outlet for the works he and his biometrical school generated. Under Galton's generous financial support, Pearson transformed his relatively informal group of followers into an established research institute. Although he was interested in eugenics, he tried to do objective research using statistical methods and separated his institute from the social concerns of the Eugenics Education Society.

Pearson's emphasis on the statistical relevancy to the problems of biology had very few audiences. Mathematicians despised new endeavor to develop statistical methodology, and biologists thought mathematicians

had no business meddling with such things. In 1903 Pearson wrote Galton that there were only two subscribers of *Biometrika* in Cambridge, one a personal friend of Pearson and one of Weldon. Even though his major contributions were correlational methods and chi-square goodness-of-fit test, in 1906 the *Journal of the Royal Society* refused to publish a paper because they failed to see the biological significance of a correlation coefficient. In 1911 after Galton's death, Pearson became the first Galton Professor of Eugenics at University College, London.

Pearson also attempted to build an intellectual bridge to medicine by applying the statistical methods he developed. During his lifetime, the medical profession was divided about their opinion of the usefulness of statistical reasoning. Clinicians who continued to emphasize the "art" of medicine thought that statistics added little information beyond that supplied by experience. Those who argued for the existence of a "clinical science," basing diagnosis on physiological instruments or bacteriological observation, saw statistics as a way to make observation more objective, but that did not consider that as "scientific" evidence.

6. The Beginning of Medical Statistics

Major Greenwood (1880–1949) was first to respond to Pearson's "crying need" for the medical profession to appreciate the importance of new statistical methods. At the age of 18, he entered medical school and read Pearson's *Grammar of Science*. He wrote to Pearson and applied statistical analyses to his research data while a student at London Hospital. During the academic year 1904–1905, after obtaining his license to practice medicine and publishing an article in *Biometrika*, he chose to study under Pearson. Despite Pearson's warning about the difficulty of earning a living as a biometrician, Greenwood decided to stake his professional career on the application of mathematical statistical methods to medical problems.

In debating with the bacteriologist Sir Almroth Wright (1861–1947) about the efficacy of vaccine therapy and a statistical measure called "opsonic index," Greenwood invoked the distinction between functional and mathematical error.[24] The former concerned errors in techniques of measurement, while the latter concerned inferential errors derived from the fact that data were a sample of population. When he pointed out that Wright had committed mathematical error, he got the attention of the medical community.[25] Consequently the Lister Institute for Preventive Medicine in 1903 created the first department of statistics and named him

its head. Greenwood characterized his department as dealing with problems of epidemiology and pathology, in contrast to Pearson's department at the University College, which dealt with heredity, eugenics and pure mathematical statistics. By training Greenwood, Pearson had helped to create the role of medical statistician, who as a researcher, understood both medical results and statistical methods.

Greenwood left the Lister Institute in 1920 for a position at the Ministry of Health and became affiliated with the newly created Medical Research Council (MRC). He saw his position at the medical establishment as instrumental in furthering the impact of statistical methods. Raymond Pearl (1879–1940) was Greenwood's American counterpart. He went to London to study under Pearson after finishing his PhD in biology at the University of Michigan. In 1918 Pearl began a long-standing relationship with The Johns Hopkins University as professor of biometry and vital statistics in the School of Hygiene and Public Health and as statistician at The Johns Hopkins Hospital.

By the early 1920's, Greenwood was not alone in arguing for application of modern statistics in medicine. One writer said in *the Journal of the American Medical Association* in 1920 that statistics was of great practical significance and should be required in the premedical curriculum.[26] Pearl in a 1921 article in the *Johns Hopkins hospital Bulletin* said that quantitative data generated by the modern hospital should be analyzed in cooperation with expert statistician. The arguments for using statistics in medicine were framed in terms of ensuring that medical research become "scientifically" grounded.[27]

7. Randomization in Experimentation

Besides Pearson, another founder of modern statistics was Sir Ronald A. Fisher (1890–1962). He also majored in mathematics at Cambridge and studied the theory of errors, statistical mechanics, and quantum theory.[28] By the age of 22, he published his first paper in statistics introducing the method of maximum likelihood, and three years later he wrote another paper deriving the exact sampling distribution of the Pearson correlation coefficient. He was also interested in applying mathematics to biological problems. Beginning in 1919, he spent many years at Rothamsted Experimental Station and collaborated with other researchers. He developed statistical methods for design and analysis of experiments, which were collected in his books *Statistical Methods for Research Workers*[29] and

The Design of Experiments.[30] He proposed three main principles — the essentiality of replication and randomization, and the possibility of reducing errors by appropriate organization of the experiment.

Fisher's major contribution to science was using randomization to do experiments so that the variation in the data could be accounted for in the statistical analysis, and the bias of treatment assignment could be eliminated. Greenwood characterized Fisher's ideas as "epoch-making" in an article published in 1948, the year before Greenwood's death. For Fisher, statistical analysis and experimental design were only two aspects of the same whole, and they comprised all the logical requirements of the complete process of adding to natural knowledge by experimentation.[30] In other words, in order to draw inference, statisticians had to be involved in the design stage of experiments. Fisher, when addressing the Indian Statistical Congress in 1938, said, "To call in the statistician after the experiment is done may be no more than asking him to perform a post-mortem examination: he may be able to say what the experiment died of".

In addition to the new developments in statistical theory brought about by Fisher's work, changes within the organization of the MRC also facilitated the emergence of the modern clinical trial. Sir Austin Bradford Hill (1897–1991), one of Greenwood's proteges, was the prime motivator behind these Medical Research Council trials. He learned statistical methods from Pearson at University College and in 1933 became Reader in Epidemiology and Vital Statistics at the London School of Hygiene and Tropical Medicine, where Greenwood became the first professor of Epidemiology and Public Health in 1927. In 1937 the editors of *The Lancet*, recognizing the necessity of explaining statistical techniques to physicians, asked Hill to write a series of articles on the proper use of statistics in medicine. These articles were later published in book form as *Principles of Medical Statistics*.[31] Upon Greenwood's retirement in 1945, Hill took his place both as honorary director of MRC's Statistical Research Unit and as professor of medical statistics at the University of London.[32]

8. First Randomized Controlled Clinical Trial

The British Medical Research Council in 1946 began the first clinical trial with a properly randomized control group trial on the use of streptomycin in the treatment of pulmonary tuberculosis. This trial was remarkable for the degree of care exercised in its planning, execution and reporting. The trial involved patient accrual from several centers, and patients were randomized

to two treatments — either streptomycin plus bed-rest, or bed-rest alone. Evaluation of patient X-ray films was made independently by two radiologists and a clinician. This blinded and replicated evaluation of a difficult disease end-point added considerably to the final agreed patient evaluation. Both patient survival and radiological improvement were significantly better on streptomycin.[33]

Hill's work set the trend for future clinical trials where both the insight of physicians and the statistical design of professional statisticians were combined. The convergence of these two separate disciplines constituted the *sine qua non* for the emergence of the probabilistically informed clinical trials. The Laplacian vision of the determination of medical therapy on the basis of the calculus of probability had finally found fulfillment.

Hill, a non-physician, acknowledged that the medical profession was responsible for curing the sick and preventing disease, but he emphasized that experimental medicine had the third responsibility of advancing human knowledge, and the statistically guided therapeutic trial was a useful way to discharge that responsibility. Unlike earlier advocates of statistical application in medicine, Hill's work became a rallying cry for supporters of therapeutic reform on both sides of Atlantic. Among many factors that contributed to this groundswell of support, one was the proliferation of new and potent industrially produced drugs in the postwar era. Supporters argued that randomized controlled clinical trials would permit the doctors to select the good treatment and prevent undue enthusiasm for newer treatments.

To those critics who believed in the uniqueness of the individual, whether patient or doctor, LJ. Witts, Nuffield Professor of Clinical Medicine of Oxford University, said in a conference in 1959, that neither patients nor doctors were as unique as they might have wanted to believe. Witts conceded that there was a conflict of loyalties between the research for truth and the treatment of the individual. However, he pointed out that similar conflict existed between the teaching of clinical students and the treatment of the patient.[34] At the same conference, Sir George Pickering, Regius Professor of Medicine at Oxford, praised the randomized controlled clinical trials and declared that, in contrast, clinical experience was unplanned and haphazard, and physicians were victims of the freaks of chance.[35]

Americans were not slow in following the British lead in applying statistics to controlled clinical trials. Americans carried out the largest and most expensive medical experiment in human history. The trial was done in 1954 to assess the effectiveness of the Salk vaccine as a protection against paralysis or death from poliomyelitis. Close to two million children

participated, and the immediate direct cost was over 5 million dollars. The reason for such a large trial was that the annual incidence rate of polio was about 1 per 2000. In order to show that vaccine could improve upon this small incidence, a huge trial was needed. Originally, there was some resistance to the randomization, but finally about one quarter of the participants did get randomized. This randomized placebo controlled double-blind trial finally established the effectiveness of the Salk vaccine.[36]

9. Government Regulation and Statistics

Later in the early 1960s, the drug Thalidomide caused an outbreak of infantile deformity. The US FDA subsequently discovered that over two and a half million tablets had been distributed to 1,267 doctors who had prescribed the drugs to 19,822 patients, including 3,760 women of childbearing age. This evidence raised the question whether the "professional judgement" of the medical community could still be trusted. The outcry from the public led the US Congress to pass the Kefauver–Harris Bill, known as the Drug Amendments of 1962 and signed by President Kennedy on October 10, 1962. This law fundamentally altered the character of research both for the drug industry and for academic medicine. It transformed the FDA into the final arbiter of what constituted successful achievement in the realm of medical therapeutics. The FDA institutionalized clinical trials as the standard method for determining drug efficacy. By the late 1960s the double-blind methodology had become mandatory for FDA approval in the US, and the procedure had become standard in most of the other Western countries by the late 1970s.

The application of statistics in medicine has scientific authority and is seen as rising above individual opinions and possessing "objectivity" and "truth." The emergence of the randomized controlled clinical trials could be seen as a special case of a more general trend — the belief that "quantification is science." This also coincided with the change of definition about statistics as a discipline. In a book written by Stanford professors Chernoff and Moses in 1959, they said, "Years ago a statistician might have claimed that statistics deals with the processing of data. Today's statistician will be more likely to say that statistics is concerned with decision making in the face of uncertainty."[37]

Through the work of Hill, the father of the modern clinical trial, statistical methods slowly were adapted in medical research. The reason that clinical trials gained legitimacy was because that public at large

realized that the decisions of the medical profession had to be regulated. Only when the issue of "medical decision making" was removed from the confines of professional medical expertise into the open arena of political debate could the statistical methods gain such wide acceptance. This ascendancy of the clinical trial method reflected the close connection between procedural objectivity and democratic political culture.

Above is the evolutionary history of statistical thinking in medicine. Medical research is much more than therapeutic research, but all medical research must lead to improvement of therapeutics or prevention. From this history one can see how the application of numerical methods in medicine has been debated throughout the past two hundred years. It shows that it took a long time for good concepts and procedures to prevail in science. The debates described could be applicable to the current problems about therapeutic research in alternative and complimentary medicine. Only through learning from past experience non-orthodox medicine can be modernized quickly.

10. Epilogue

Early landmarks in clinical investigation anticipated the current methodology.[38] For example, James Lind (1716–1794) in 1753 planned a comparative trial of the most promising treatment for scurvy. However, most pre-twentieth century medical experimenters had no appreciation of the scientific method. Trial usually had no concurrent control, and the claims were totally subjective and extravagant. The publication by Benjamin Rush (1745–1813) in 1794 about the success of treatment of yellow fever by bleeding was one example.

Statistics was very influential in the development of population genetics. Johann Gregor Mendel (1822–1884), a monk in the Augustinian order, studied botany and mathematics at the University of Vienna. He carried out experiments on peas to establish the three laws of genetics — uniformity, segregation and independence. After Darwin advanced the theory of evolution, there was a great debate between the evolutionists (biometricians) and those believing in the fixation of species (Mendelians). Pearson in his series of papers, *Contributions to the Mathematical Theory of Evolution, I to XVI*, gave mathematical form to the problems of genetics and evolution. However, he held the view of continuous change and never accepted Mendelism.[39]

After reading Pearson's papers while a student at Cambridge, RA Fisher made major contributions to the field of genetics, especially he synthesized and reconciled the fixed inheritance theory of Mendel and the gradual evolution theory of Darwin.[40] He was considered as one of three founders of the population genetics, together with Sewall Wright and JBS Haldane, and he occupied an endowed chair of genetics at Cambridge University. Fisher's major contributions were the theoretical foundation of statistics including estimation and the testing of hypotheses, exact distributions of various statistics, and statistical models of natural phenomena.[41]

As mentioned in the debates between the numerical methods school and the physiological school, physiological measurement data were collected using precise instruments during the later half of the nineteenth century in conjunction with the creation of research universities. Statistical methods were developed to analyze the data coming from the laboratories. Later, the controversy between the biometrical school and the bacteriologists/immunologists in the laboratory led to the further developments of correct statistical methods to analyze laboratory data.

Before the development of modern epidemiology, John Graunt (1620–1674) started to collect data on mortality, derived the life table based on survival, and thus created the discipline of demographic statistics. William Farr (1807–1883) further improved the method of the life table and created the best official vital statistics system in the world for the Great Britain.[38]

In 1848, John Snow (1813–1858) carried out the first detailed investigation of the cholera epidemic of London. Development of the discipline of bacteriology was associated with the investigation of epidemics due to infectious agents. Mathematics and statistics were used in modeling and analysis of infectious epidemic data. Modern statistical methods were developed to investigate the epidemics of non-infectious diseases in the last half of the 20th century. Epidemiological research has become another field of statistical application. It has merged with statistical survey methods to carry out surveillance and disease monitoring, and it is called population science, in contrast to clinical and laboratory sciences.

In every field of medical research, statistical thinking and methods are used to provide insight to the data and to verify the hypotheses. The generation of new data and new hypotheses also propel developments of new statistical methodology. In the twentieth century, modern statistics as created by Pearson and Fisher has made a huge impact on the advancement of human knowledge, and its application to medicine richly demonstrates the importance of statistics.

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