DERLEME REVIEW

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To be Together Medicine and Biostatistics in History: Review

Tarihte Tıp ve Biyoistatistiğin Buluşması

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ABSTRACT Today, statistics in health sciences, especially in the medical field are known to be indispensable. However, in some periods of scientists claiming mutually justified by them, medicine and statistics are not met, they argued as well that the majority of scientists are advocating the opposite. In this study, the time and history to reach biostatistics is indispensable, were investigated. In the period preceding the date based on the Old Testament, the first clinical trial conducted by Daniel the prophet is accepted that. In the 17th and 18th centuries laid the foundation of modern statistics, and then began to be used, especially in the health field. The rise of biostatistics in the 19th and 20th century is considered one of the most important developments in terms of humanity. With Sir Francis Galton and Karl Pearson's studies, statistics has been removed from being a social science, and turned into an applied science and data collection how important and statistics in medicine necessarily need to be used has been proven. Later, biostatistics and consequently the establishment of associations that uses a combination of medicine and biostatistics begin publication of articles with the importance of this issue has been fully realized. Today, the introduction of statistics that has been recognized that health is the scientific study and 1950's been around for years all over the world are taught as a compulsory subject in schools of medicine biostatistics.

Keywords: Biostatistics; history of medicine; history, ancient; history, 17th century; history, 18th century

ÖZET Günümüzde istatistiğin tüm sağlık bilimlerinde, özellikle tıp alanında vazgeçilmez olduğu bilinmektedir. Ancak bazı dönemlerde bilim insanları karşılıklı olarak kendilerince haklı sebepler öne sürüp, tıp ve istatistiğin bir araya gelemeyeceğini ileri sürmüşlerdir, bunun yanı sıra tam tersini savunan bilim insanları da çoğunluktadır. Bu çalışmada, bu dönemlerden günümüzdeki vazgeçilmezliğe nasıl ulaşıldığının tarihçesi incelenmiştir. Tarihten önceki dönemlerde Tevrat'a dayanılarak, ilk klinik denemenin peygamber Daniel tarafından yapıldığı kabul edilmektedir. Daha sonra istatistik ve tıp, Yunan bilim adamları tarafından bir araya getirilmeye çalışılmıştır. 17. ve 18. yüzyılda modern istatistiğin temelleri atılmış, sonraları özellikle sağlık alanında kullanılmaya başlamıştır. Claude Bernard, tıbbın bilimsel olması için olasılıklara değil, gerçeklere dayanması gerektiğini iddia ederek, doktorların istatistiği reddetmeleri gerektiğini öne sürmüştür. Matematikçilerin prensi olarak bilinen Alman bilim adamı, Carl Friedrich Gauss ise, Bernard'ın teorisinin tersini savunarak olasılık teorisi ve sayısal yöntemlerin tıp ve klinik yöntemler de dahil olmak üzere, tüm bilimsel disiplinlerde gerekli olduğunu savunmuştur. 19. ve 20. yüzyılda biyoistatistiğin yükselişi, insanlık açısından en önemli gelişmelerden birisi sayılmaktadır. Biyoistatistiğin babası olarak kabul edilen İngiliz bilim adamı Sir Francis Galton ve Karl Pearson'ın çalışmaları ile istatistik bir sosyal bilim olmaktan çıkartılarak matematik uygulamalı bir bilim haline getirilmiş ve veri toplamanın ne kadar önemli olduğu ve istatistiğin tıpta mutlaka kullanılması gerektiği kanıtlanmıştır. Daha sonraları, biyoistatistik derneklerinin kurulması ve bunlara bağlı olarak tıp ve biyoistatistiği bir arada kullanan makalelerin yayımlanmaya başlaması ile konunun öneminin tamamen farkına varılmıştır. Günümüzde istatistiğin girmediği sağlık çalışmalarının bilimsel olmayacağı kabul edilmiştir ve 1950' li yıllardan beri dünyadaki tüm tıp fakültelerinde biyoistatistik zorunlu ders olarak okutulmaktadır.

Anahtar Kelimeler: Biyoistatistik; tıp tarihi; tarih, eski; tarih, 17inci yüzyıl; tarih, 18inci yüzyıl

Today we live in the golden age of biostatistical science. Health researchers are proud to statistical thinking and practices. Laboratory science, clinical research and epidemiological studies, statisticians do collaborations are sought. Many medical journals, statisticians are asked to serve as reviewers. In many countries Institutes of Health, a statistician at every stage of research and studies are needed. Pharmaceutical companies, pharmaceutical development, the research from design, analyze data, and to prepare reports they need a biostatistician. Use of biostatistics, 21^{th} century, clinical trials, survival analysis, and statistical genetics has been compulsory for. The statistical thinking is inevitable for all medical research and health policy. But in the beginning it was not so. In this article, the history of the development of statistical thinking in the medical field has been studied.[1-3]

WHY THE MEDICINE NEEDS STATISTICS

It is human nature to try to convert observations into knowledge. Also recognize the samples and interpret observations are in human nature. Accordingly, a definition of biostatistics could be to convert biological information into knowledge. However, we argue that this is too broad a definition because observations often mislead and our intuitions are often wrong. Starting from this idea biostatistics defined as follows.

Biostatistics is the discipline concerned with how we ought to make decisions when analyzing biomedical data. It is the evolving discipline concerned with formulating explicit rules to compensate both for the fallibility of human intuition in general and for biases in study design in particular.[4]

Even if they do not carry out research themselves, most doctors need to read and interpret the published research of others. Papers in medical journals are full of the results of statistical analyses, and the validity of the results of these studies depends on the appropriateness of the design of the study. Given the widespread use of statistical techniques in medicine, no-one could do this without understanding the fundamentals of statistics. Even drug company literature increasingly contains statistical material. Also, diagnostic tests are used by doctors to do should be proven by statistical analysis.[5,6]

MEDICINE AND STATISTICAL SCIENCES IN BC

One of the most ancient of all biometric problems is that of the design of clinical trials. The Bible's Old Testament, in the first chapter of the Book of Daniel, tells of how the young Daniel and three compatriots were sent to the court of King Nebuchadnezzar to wait for an audience with the king. The king furnished them with a rich diet of meat and wine, and Daniel was faced with a dilemma-he and his men did not want to depart from their kosher diet, but how could they refuse to eat the king's meat without causing offense? Daniel proposed a clinical trial to the king's representative Melzar, like this;

"Prove thy servants, I beseech thee, ten days; and let them give us pulse to eat, and water to drink. Then let our countenances be looked upon before thee, and the countenance of the children that eat of the portion of the king's meat: and as thou seest, deal with thy servants. So he consented to them in this matter, and proved them ten days. And at the end of ten days their counte-nances appeared fairer and fatter in flesh than all the children which did eat the portion of the king's meat. Thus Melzar took away the portion of their meat, and the wine that they should drink and gave them pulse. This account, which describes events from 606 B.C., is not adequate in all respects. Quality control questions about the study: Was there a stopping rule? Why ten days? What was the outcome measured ("fairness") was there a discrete or continuous scale employed? How were the inferences summarized? The evidence was used to change state policy and Daniel and his companions were allowed to continue their cosher diet red meat is bad for one's health. This experiment can be considered as the first clinical trial (606 B.C.).[7,8]

The other important character of the history of biometry is Asclepiades in the second century B.C. Asclepiades is a Greek doctor (129-91 B.C.), born in Bithynia, now part of northwestern Turkey, and probably died in Rome. His treatments departed from the teachings of Hippocrates, and they were extremely popular. He prescribed exercise, a forgiving diet, music, and plenty of wine. He may have invented the shower bath. Asclepiades rejected any appeal to empirical medicine that was not guided by theory (his theory); he made no appeal to measurement or use of statistics.[9,10]

Asclepiades's doctrines were so attractive that, more than two centuries after his death, the great Galen of Pergamum (129-200 A.D.) felt it necessary to denounce him. Without Asclepiades, Galen might never have written what might be called the first book on biometry. Claudius Galen was born in Pergamum (modern-day Turkey) of Greek parents. He was a physician, writer and philosopher who became the most famous doctor in the Roman Empire and whose theories dominated European medicine for 1,500 years. Galen was a prodigious author, and wrote some 80 different medical treatises. Unfortunately, some of his work was destroyed in a fire in the 2nd century, but what remains is a valuable history of medicine. One of them which is considered as the first book of biometry is "Galen on Medical Experience. First Edition of the Arabic Version with English Translation and Notes. By R. WALZER. Published for the Trustees of the Late Sir Henry Wellcome by the Oxford University Press, London, 1944".[8]

MEDICINE AND STATISTICAL SCIENCES IN 17. AND 18. CENTURY

The origin of modern statistics can be traced back to the seventeenth century. One of theme related to political science and developed as a quantitative description of the various aspects of the affairs of a government or state. This subject also became known as political arithmetic. Taxes and insurence caused people to become interested in problems of censuses, longevity, and mortality. Such consideration assumed increasing importance, especially in England, as the country prospered during the development of the empire. John Graunt (1620-1674) and William Petty (1623-1687) were early students of vital statistics, and others followed their footsteps. John Graunt, a British merchant, categorized the cause of death of the London populace using statistical sampling, noting that "considering that it is esteemed an even lay, whether any man lived 10 years longer, I supposed it was the same that one of any 10 might die within one year." Graunt's statistics can be compared to recent data from the United States in 1993, as a result of this work, the government of the United Kingdom set up the first government-sponsored statistical sampling service.[5,11,12]

At about the same time came the development of the second root of modern statistics: the mathematical theory of probability engendered by the interest in games of chance among the leisure classes of the time. Important contributions to this theory were made by Blaise Pascal (1623-1662) and Pierre de Fermat (1601-1665), both Frenchmen. Jacques Bernoulli (1654-1705), a Swiss, laid the foundation of modern probability theory as Ars Conjectandi, published post-humously. Abraham de Moivre (1667-1754), a Frenchman living in England, was the first combine the statistics of his day with probability theory in working out annuity values. De Moivre also was the first to approximate the important normal distribution through the expansion of the binomial.[11]

Modern times for our subject seems to have begun with John Lind (1716-1794) some 240 years ago (late 1730's). Lind, a Scottish naval surgeon, decided to do a comparative trial of the then current 'cures' for scurvy. He took 12 cases of scurvy out to sea. They were all put in the same area devoted to the sick and all were given a common diet. He divided the patients into six groups of two each. Each of five pairs was treated with a different therapy used at various times. One set of two was fed two oranges and a lemon every day. To quote: 'The consequences were that the most sudden and visible good effects were perceived from the use of the oranges and lemons'. It is of interest that it took the British Navy 40 years to supply oranges, lemon and lime juice to its sailors at sea. That was how long it took for the Lords of the Admiralty to accept Lind's results. One can imagine the goings-on in the Advisory Councils to the Admiralty at the time; Lind was a misguided clinician, he had no statistical advice; how can you arrive at a definitive conclusion with such small numbers. The only thing missing is the recommendation that they needed more evidence-another trial with much larger numbers, which if performed would have eliminated scurvy in the British Navy some 39 years earlier. Lind was primarily a clinician and there is no record of his having theorized on the method.[13-15]

French physiologist Claude Bernard (1813-1878), argued that for medicine to be truly scientific, it must be "based only on certainty, on absolute determinism, not on probability". Bernard was skeptical about statistics and believed that it was not a science, "Statistics can never yield scientific truth." He went on to urge doctors "to reject statistics as a foundation for experimental therapeutic and pathological science".[1,16]

In contrast, the French mathematician Pierre-Simon Laplace (1749-1827) and Carl Friedrich Gauss (1777-1855) in Germany, who sometimes referred to as the Prince of Mathematicians, among others, advocated that probability theory and numerical procedures could be useful in all scientific disciplines, including medicine and clinical tests.[16]

English physician Francis B. Hawkins (1796–1894) foresaw the need for statistics in medicine, and told that, "Medical statistics affords the most convincing proofs of the efficacy of medicine". French mathematician Pierre-Simon de Laplace (1749-1827) claimed that our knowledge was full of uncertainties, and believed that the probability theory could be applied to the entire system of human knowledge. Based on the probabilistic argument, Laplace and other researchers, particularly Pierre-Charles-Alexandre Louis (1787-1872) and Louis Denis Jules Gavarret (1809-1890), introduced statistics in medicine. Louis actually reached his conclusions from relatively small numbers and applied some numerical methods of medical analysis, and also Gavarret demonstrated in 1840 how to apply sophisticated mathematical concepts to medicine.[12]

Perhaps the earliest important figure in biometric thought was Adolphe Quetelet (1796-1874), a Belgian astronomer and mathematician, who combined the theory and practical methods of statistics and applied them to problems of biology, medicine, and sociology. Quetelet showed how higher mathematics could become an integral part of applied statistics. Largely through his demonstrations, for example, the bell shaped graph of the normal distribution of variations from the median eventually became almost as familiar to those working for social, political, and medical change as it had been to mathematicians.[11,12,17]

MEDICINE AND STATISTICAL SCIENCES IN 19. AND 20. CENTURY

Until the rise of biostatistics in the 19th century, case histories were perhaps the main stay of clinical reasoning in medicine. Physicians interested in learning more about the naturalistic course of abnormal behavior and mental functioning developed the case history approach into a highly interpretative form.[18]

Rise of biostatistics in this 20th century, like that of geometry in the 3rd century before Christ, can be considered as one of the most important critical periods in the advance of the human understanding.[19]

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. Galton has been called the father of biometry and eugenics (a branch of genetics), two subjects that he studied interrelatedly. 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. 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, influenced by his own motto:"Whenever you can, count" seldom went for a walk or attended a meeting or lecture without counting something.[20,21]

Galton accepted the evolutionary doctrine that the condition of the human species could be improved most efectively 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.[1,11,19]

A contemporary of Galton's, Florence Nightingale (1820-1910), was the first distinguished female statisticians. In addition to being the founder of modern nursing, for which she is universially famous, she was an excellent mathematician who pioneered the compilation and graphic presentation of vital and medical statistics.[11]

Karl Pearson, at University College, London, became interested in the application of statistical methods to biology, particularly in the demonstration of natural selection, through the influence of W.F.R. Weldon (1860-1906), a zoologist at the same institution. Weldon, incidentally, is credited with coining the term biometry for the type of studies he pursued. Pearson continued in the tradition of Galton and laid the foundation for much of descriptive and correlation statistics and also changed statistics from a descriptive to an inferential discipline. He became professor of mathematics at King's College, Cambridge in 1881. After Cambridge, he studied German literature, read law and was admitted to bar. 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 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.

As statistician, Pearson emphasized measuring correlations and fitting curves to the data, and for the latter purpose he developed the new chi-square distribution. Rather than just dealing with mathematical theory, Pearson's papers most often applied the tools of statistics to scientific problems. With the help of his first assistant, George Udny Yule, Pearson built up a biometric laboratory on the model of the engineering laboratory at University College. They measured skulls, gathered medical and educational data, calculated tables, and derived and applied new ideas in statistics. 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, which is known as the first journal of modern statistics. 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. In 1911 after Galton's death, Pearson became the first Galton Professor of Eugenics at University College, London.[20]

THE BEGINNING OF MEDICAL STATISTICS

Major Greenwood (1880-1949), the first name being his family Christian name and bearing no military significance, was drawn unwillingly into medicine by his father and trained at the London Hospital. With no desire to practise, he moved through physiological research and a mathematical training at University College to the natural conclusion, a career in medical statistics. 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.

After a period of study with Karl Pearson he was appointed statistician to the Lister Institute in 1910. In 1919 Greenwood joined the newly created Ministry of Health with responsibility for medical statistics. The Royal Society awarded the Buchanan Medal to Greenwood in 1927, and elected him a Fellow in 1928. He was elected President of the Royal Statistical Society in 1934 and awarded its Guy Medal in Gold in 1945.

Greenwood produced a large body of research, was the first holder of important positions in modern medical statistics and wrote extensively on the history of his subject, he wrote in his obituary, "in the future, it may well indeed seem that one of his greatest contributions, if not the greatest, lay merely in his outlook, in his statistical approach to medicine, then a new approach and one long regarded with suspicion. And he fought this fight continuously and honestly-for logic for accuracy, for 'little sums.'". The Greenwood statistic was used to discover that there is some kind of order in the placement of genes on the chromosomes of living things and this inspired a new look at epigenetics, which is now considered to be equally as important as genetics in how living organisms develop and evolve.

Pearsonian methods to study biomedical phenomena; another prominent follower was John Brownlee (1868-1927) was a British statistician who published important papers in biometry and was an exponent of "the statistical method". Brownlee utilized Pearson's insight that the Gauss-Laplace or normal distribution curve was, in fact, just a particular case of an entire family of frequency distribution systems.[1,22-24]

In the field of biostatistics specifically, Pearson is remembered for engaging in a dispute with Alrmoth Wright (1861-1947) over the meaning of the statistics Wright had collected to demonstrate that antityphoid inoculation reduced the chance of infection for soldiers in the British Army. In critiquing Wright's conclusions, Pearson made use of one of the statistical constructs for which he is remembered today, namely the correlation coefficient, which was designed to measure the degree of association between two phenomena.[22]

By the early 1920's, Greenwood was not alone in arguing for application of modern statistics in medicine. Kilgore (1920) noted that statistics was of great practical significance and should be required in the premedical curriculum. He had published a paper which the name is "relation of quantitative methods to the advanced of medical science" in 1920, and studied about "percentage of quantitative reports in various medical journal" in this paper.[25] 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. 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 becomes "scientifically" grounded.[1,16]

Besides Pearson, another founder of modern statistics was Sir Ronald A. Fisher (1890-1962). He was the dominant figure in statistics and biometry in the twentieth century. In 1948, Fisher called biometry "the active pursuit of biological knowledge by quantitative methods". His many contributions to statistical theory will become obvious.[1,11,26]

Fisher also majored in mathematics at Cambridge and studied the theory of errors, statistical mechanics, and quantum theory. 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 and The Design of Experiments. 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. 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"*.[1,11,26]

Austin Bradford Hill (1897-1991) was another statistician who in 1937 published a series of articles in the *Lancet* on the use of statistical methodology in medical research. In 1947 he published a simple commentary in the *British Medical Journal* calling for the introduction of statistics in the medical curriculum. He called for physicians to bewell versed in basic statistics and research study design in order to avoid the biases that were then so prevalent in what passed for medical research. Bradford Hill went on to direct the first true modern randomized clinical trial. 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. 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.[1,11,24,26]

In 1954, the *British Medical Journal* published "Numbering Off", the proceedings of a debate sponsored by the Royal Statistical Society on the growing application and influence of statistics in medicine.[16] Dr. R.A.J.Asher suggested that statistics should be welcome as they influenced all branches of medical sciences and life itself. Mr. R. S. Murley opposed the motion. He found it impossible to disagree entirely with Dr. Asher, but pointed out that the motion referred to all branches of medicine. Medicine was an art, statistics a science; he conceded that latter had its uses, but when it came to mixing science and art, statistics was as out of place as a skillet in a Crown Derby tea-service". He concluded "statistics might be well for the elite but were a menace to the mob". Another speaker "referred darkly to the deliberate misuse of statistics, fostered - for what purpose? - by statisticians themselves. "Statistical publications", he said, "could be recognized by the prolixity of their tables. In his view no papers should contain any tables at all". The debate concluded with the motion that the influence of statistics should be welcomed in all branches of medicine and this was carried by a narrow majority on a show of hands.[16,17]

Years after the publication of "Numbering Off", significant changes have occurred in statistics, biostatistics and the interface of these disciplines. From that time until this day have seen a great deal of activity and an explosive growth in the development of biostatistics that shows no sign of abatement as Hopkins (1958) stated that "biostatistics is here to stay as an essential part of the medical school curriculum". Some commentators believe that the development of statistics in the 19th century might have had a bigger influence on the practice of medicine than the development of antibiotics. During the 20th century, particularly in the latter half, a marked progress had been made; clinical research methods had improved significantly and new methods were developed as the use of statistical techniques continued to increase. Clinicians and health policy leaders were asking for statistical evidence that a certain intervention was effective.[16]

THE FUTURE OF BIOSTATISTICAL SCIENCES

In 1982, Zelen looked into the future of biostatistics and biostatistical science as a discipline, so there is an opportunity to take a retrospective look at how good his predictions have been, with an eye toward making further predictions for the new millennium. Zelen noted the emergence of a field that he called "biostatistical science" referring to the applications of statistics, probability, computing and mathematics to a subject matter field. Explicit in the definition was his view that the biostatistician is acting as a scientist and must possess expertise in the subject matter field. He questioned whether "biostatistics" or "biometrics" was a discipline, since either term referred to a collection of statistical techniques which are primarily used in applications to the biological and biomedical sciences. In the discussion of the paper, BG Greenberg and SW Greenhouse disagreed with Zelen's characterization of biostatistics, arguing that indeed biostatistics is a discipline and that biostatisticians are scientists. Also Zelen said that, "The future of Biostatistical Science will be intimately related to computing". 25 years later (2006) he still hold the same view on the role of computing-not only in Biostatistical Science, but also in Statistical science. In 1982, he had described the history of development of statistical software in four stages. The final stage, referred to as 'stage IV' described automatic data analysis systems.[3,27]

Gehan (2000) said that, in the twenty-first century those biostatisticians becoming biostatistical scientists will be leaders, whereas those biostatisticians not becoming experts in a subject matter field will be technicians, perhaps to be replaced by subject matter experts who learned some biostatistics and appropriate ways to make computations. Also, he said that "I hope that Proffessor Zelen is wrong in predicting linkage of the growth in biostatistics to the growth in computing. Both will undoubtely grow in volume and complexity, but computer expansion may not promote biometry or biostatistics *per se.* In fact, the concentration by statisticians on improving computer hardware and especially software sometimes tends to inhibit creative thinking in statistical methodology. The computer should remain a tool and not the main concern of the biostatistician". In the twenty-first century those biostatisticians becoming biostatistical scientists will be leaders, whereas those biostatisticians not becoming experts in a subject matter field will be technicians, perhaps to be replaced by subject matter experts who learned some biostatistics and appropriate ways to make computations.[28]

CONCLUSION

Knowledge of the historical development of any subject, that subject is very important in terms of the value of knowledge. Nowadays statistics, are used very effectively in the field of medicine and health care, or even scientific studies, it has become one of the imperatives of development. However, a meeting of medicine and statistics, ie statistics in the field of medicine and health has not been very easy to use, the need for health care workers as well as statisticians history in their own right have resisted reasons put forward in this regard.

What will be the place of biostatistics (and biostatisticians) in the new millennium? Biostatisticians will have to adapt to worldwide changes, growth in population, the development of large corporations, the trends emphasizing worldwide trade and economic progress over preservation of the environment, and globalization generally. However, even with all these developments, problems relating to biology, medicine, health, and the environment will remain, so biostatisticians can surely play an important role, if they are willing to adapt to changing circumstances.

The past is the best guide to the future, so comments will concentrate on those areas of most recent development that seem likely to be developed further in the coming years. With this perspective, areas considered are applications (clinical trials, epidemiology, vital statistics), philosophies, models, advances in *computing, and the profession of biostatistics.*

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Conflict of Interest

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