

# Perspectives

## Anecdotal, Historical and Critical Commentaries on Genetics

*Edited by James F. Crow and William F. Dove*

### Raymond Pearl, Smoking and Longevity

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SEWALL Wright, in his early years as a scientist, developed an algorithm for calculating inbreeding coefficients, which brought wide attention to one of the most stellar careers of 20th century genetics (WRIGHT 1922). His first population genetics problem, and its solution, are much less well known. This came when, as a graduate student, he tried to help his roommate, Harold D. Fish, solve a problem that caused considerable debate in William E. Castle's research group at the Bussey Institution of Harvard University.

Fish, a graduate student of Castle, had read with great interest an article published in the *American Naturalist* by Raymond PEARL (1913), which made the surprising claim that continued brother-sister mating did not lead to an increase in homozygosity (then called homozygosis). Pearl was a biostatistician and one of the first to tackle the early problems of population genetics from a mathematical perspective. Many of Pearl's subsequent articles aroused controversy, and this was the first to earn the ire of an entire cadre of geneticists. In short, Pearl argued that beyond the  $F_3$  generation, with brother-sister mating and no selection, heterozygosity would not decrease below 50% as it would with continued self-fertilization.

In his example, Pearl started with a cross between two homozygous lines. The  $F_1$  would be heterozygous for any loci that differed in the two lines. In the  $F_2$ , heterozygosity would be reduced to 50%. In the  $F_3$ , there would be no further reduction, the reason being that sib mating among the  $F_2$  individuals is equivalent to random mating, since all individuals are effectively sibs. Pearl's calculations had become cumbersome, so he stopped there and reached the conclusion that now seems ridiculous: that inbreeding other than self-fertilization does not necessarily decrease heterozygosity. Although Fish had read an article by Edward M. East and Herbert K.

Hayes on the subject and had a sense that inbreeding in a population would lead to increased homozygosity, no one at this point had calculated the effects of inbreeding beyond self-fertilization (PROVINE 1986).

The effects of artificial selection were a topic of great interest at the Bussey Institution. Shortly after the Institution was reorganized into a Graduate School of Applied Biology, East published a landmark article that showed that quantitative traits behaved in a Mendelian fashion (EAST 1910). Taking their cue from Darwin's concept of natural selection, East, Castle, and their students began to pursue studies designed to probe the genetic consequences of selection.

In 1914, a new graduate student in William Morton Wheeler's group at the Bussey, Phineas J. Whiting, was conducting a selection experiment with the greenbottle fly. Whiting raised the flies by allowing adults to lay eggs in decaying guinea pig carcasses, presumably left over from Castle's selection experiments. Fortunately for genetics, Whiting was able to stand the stench of this process. Many years later, Sewall Wright recalled that no one but Whiting could get within 100 feet of the shed where this took place (PROVINE 1986).

Whiting's experiment involved selection for bristle number by using brother-sister mating. He calculated that heterozygosity was reduced by one-eighth from the  $F_2$  to the  $F_3$  generation, and (incorrectly) that it would decrease by the same amount each generation thereafter. He consulted East on these calculations, who agreed that a reduction in heterozygosity must take place, but by a different magnitude. Fish became interested in testing Pearl's assertion and quantifying the amounts of heterozygosity with inbreeding. He worked out the genetic consequences of inbreeding beyond the  $F_3$  and discovered that Pearl's mistake was to assume that brother-sister mating was equivalent to random mating in all generations beyond the  $F_2$ . In performing these calculations, Fish soon had covered their room with pages of figures. Wright became interested, and, using a matrix of all possible combinations of matings with two alleles, worked out a formula for calculating the

**This Perspectives is dedicated to the late Jack Weir, a scientist and historian from the University of Kansas, whose documentation of the former Bussey Institution of Harvard has been of great value in understanding the history of genetics in the United States.**



Raymond Pearl, 1879–1940.

genetic consequences of brother-sister mating for any number of generations. Wright had solved the problem being studied by Whiting, Fish, and Pearl, and happily revealed his answer (PROVINE 1986).

Meanwhile, Pearl had corresponded with East and asked him his opinion of the unusual conclusion in Pearl's 1913 article. East then calculated the effects of continued brother-sister mating, although by a method different from Wright's, and wrote to Pearl that his conclusion was not correct. East mentioned that Fish would publish the correct answer, and Pearl became furious with Fish for pointing out his mistake in print. Pearl then reportedly came to the Bussey to ask that Fish be fired. Shortly thereafter, Pearl published a correction (PEARL 1914) and attributed the correct interpretation to East (PROVINE 1986). Thus, Raymond Pearl was indirectly responsible for Sewall Wright's entry into the field of population genetics.

Raymond Pearl was among the most productive biologists of the 20th century. He wrote on topics as diverse as poultry genetics, alcohol and life span, tuberculosis, and population control. Controversy often swirled around his findings; however, in many instances his conclusions were significant and had important implications for both the scientific community and the general public.

Pearl was born on June 3, 1879, in Farmington, New Hampshire. His family emphasized classics, and his parents and grandparents encouraged him to pursue Greek

and Latin. Enrolling at Dartmouth College at the age of 16, he was quickly diverted to Biology under the tutelage of John H. Gerould. He graduated with an A.B. in 1899, the youngest graduate in the class. Pearl was an accomplished musician and was successful in organizing friends and colleagues for amateur music performances of all kinds. He was said to be proficient at almost every wind instrument. He was also an excellent student. Writing about him many years later, Herbert S. Jennings said, "During his senior year he was assistant in the course in general biology, of which the present writer was at that time in charge. He showed at that early period the masterful and competent personality that marked him throughout life" (JENNINGS 1943, p. 296).

Pearl and Jennings attended the University of Michigan together in 1899. Pearl was an assistant in zoology while a graduate student. He participated in the Biological Survey of the Great Lakes, where he studied variation in fishes. He received his Ph.D. in 1902 working on the behavior of planarians and stayed on as instructor of zoology until 1906. He met his future wife, Maude M. De Witt, in the zoological laboratory at the University of Michigan. They were married in 1903, traveled abroad in 1905 and 1906, and worked at the University of London, University of Leipzig, and Marine Biological Station in Naples.

Shortly after his doctoral work, Pearl began to investigate statistical methods in biology and collaborated with Karl Pearson on this subject at University College, London in 1905–1906. In 1906, he became an Associate Editor, with Pearson, of *Biometrika*, an association that continued until 1910. Pearl became instructor in zoology at the University of Pennsylvania in 1906, where his primary focus was on statistical methods in biology. In 1907, he was recruited as head of the Department of Biology of the Maine Agricultural Experiment Station at the University of Maine in Orono. His work there focused on the genetics of poultry and other domestic animals. In 1915, he published two widely read books, *Diseases of Poultry* (PEARL *et al.* 1915) and *Modes of Research in Genetics* (PEARL 1915); the latter showed his fluency with biometrical approaches to genetic problems. His book *Introduction to Medical Biometry and Statistics* (PEARL 1923) was widely read and was influential for many biologists and physicians working with quantitative data.

Pearl was widely recognized as a highly productive scientist and an excellent manager. Perhaps partly for these reasons, Herbert Hoover asked him to serve as Chief of the Statistical Division of the United States Food Administration from 1917 to 1919. During these years, Pearl became interested in the economics of food, publishing widely in the area and writing a book called *The Nation's Food* (PEARL 1920). In 1918, he was recruited by Johns Hopkins University to serve as Professor of Biometry and Vital Statistics in the newly founded School of Hygiene and Public Health. There, he orga-

nized a department and laboratory of statistics (JENNINGS 1943).

Pearl was a very large and impressive person. His interest in and knowledge of biology was reportedly encyclopedic. He supported this with voluminous collections of reprints and citations in particular subjects. For example, Pearl's large collection of references on *Drosophila* was written on single sheets, about four by six inches, and bound into books. Pearl had a place on the form to check the quality of the article. His opinions of these articles were apparently on target, for Bridges' nondisjunction article was checked "good" (J. F. CROW, personal communication).

Perhaps the most remarkable thing about Pearl was the sheer scope of his scientific output. His publications, some 712 articles and more than 17 books, encompass a great deal of then modern biology. He published on animal behavior; genetics of domestic animals and plants; alcohol, tobacco, and life span; general biology of humans, including longevity and mortality; eugenics; biology of death; population growth; food and prices; vegetarianism; natural theology without theism; statistics of garbage collection; Jewish and Christian marriages; and the proper work for agricultural experiment stations, to name just a few areas (JENNINGS 1943). In 1913 alone, Pearl published 34 articles (WEIR 1994). A question regularly asked in the 1930s was: "Who is the best-read biologist?" The answer: "Raymond Pearl. He has only to read all that he has written" (J. F. CROW, personal communication).

Much of Pearl's work during the 1920s and 1930s concerned the effects of the environment (disease, alcohol, tobacco) on longevity. His 1922 book *The Biology of Death* (PEARL 1922), based on his Lowell lectures in 1920, and "Experimental studies on the duration of life" (PEARL and PARKER 1921), *The Biology of Population Growth* (PEARL 1925), and *The Rate of Living* (PEARL 1928) serve as examples of this period. His book *Alcohol and Longevity* (PEARL 1926) argued that moderate alcohol consumption was not harmful, and he based his own practice on this conclusion (JENNINGS 1943). Today, of course, the idea that moderate alcohol consumption may be beneficial for cardiovascular health is widely recognized and supported by a large body of evidence. At the time, however, prohibition was on the public's mind, and Pearl's conclusion gave rise to great controversy.

The beneficial practice of alcohol consumption was undoubtedly supported by Pearl's association with the social critic H. L. Mencken. Mencken was the organizer of the Saturday Night Club of Baltimore, a social club that featured prominent people, good food and drink, and music. Mencken and Pearl would invite Peabody Conservatory students to play in the Saturday evening sessions. At the stroke of midnight the music always stopped abruptly (in the middle of a bar perhaps) and the feast began. The impecunious Peabody students

were glad to participate and perhaps to put up with Mencken and Pearl's playing, which was said to be louder and more enthusiastic than technically proficient, to eat what was probably their only square meal of the week.

In 1938, Pearl's study on the effects of tobacco and longevity also caused controversy. After his studies showed that smoking decreases longevity but drinking does not, Pearl announced that he was going to stop smoking and drink more than ever. Despite his often provocative pronouncements, the proof that Pearl provided that smokers are prematurely killed by the effects of tobacco must be recognized as one of his most important achievements in epidemiology.

In fact, Pearl's 1938 article in *Science* (PEARL 1938) describing the premature death of smokers was the first significant piece of data on the link between tobacco and longevity. The data were collected from more than 7000 people over the age of 35 who had smoked, and it pointed very clearly toward significant reductions in life span for moderate and heavy smokers. Although Pearl's article was cited in several scientific publications in the years that followed, the U.S. public did not become aware of the importance of this relationship for several decades. Pearl was in a unique position to appreciate the epidemiological significance of these findings and was far ahead of his time in appreciating their importance for public health. However, it was not until the 1964 Surgeon General's report on the negative health consequences of smoking that this information began to seep into the public consciousness (ANONYMOUS 2002b).

As part of his work on longevity, Pearl studied the biology of particular diseases, including tuberculosis, cancer, influenza, pneumonia, heart disease, and encephalitis. This work was widely cited and highly influential, but it led to at least one difficulty for Pearl that might not otherwise have been anticipated. One of Pearl's strongest critics was the Harvard mathematician Edwin B. Wilson, who like Pearl was born in 1879 and completed his undergraduate work at a young age. After earning his Ph.D. from Yale in 1901, Wilson joined the faculty of mathematics at Yale and, eventually, was recruited to the Department of Physics at the Massachusetts Institute of Technology in 1907. His position, like Pearl's, was as Professor of Vital Statistics in the School of Public Health. Wilson had an extremely distinguished career in science and was elected to the National Academy of Sciences in 1919. In 1922, he cowrote a textbook on mathematical physics with Josiah Willard Gibbs, the founder of statistical thermodynamics (WILSON and GIBBS 1922). He was President of the Social Science Research Council and President of the American Statistical Association (WEIR 1993). He served as editor of the *Proceedings of the National Academy of Sciences* for 50 years. Coincidentally, Pearl had been elected to the National Academy in 1916 and served as the

Chairman of the Editorial Board of the Academy's journal.

Wilson was very concerned with what he called the "professional ethics of applied mathematics" (WEIR 1993). By this, he meant that great care should be taken to assure that the mathematical treatment of biological data (or, for that matter, data from any field) be carried out properly. As more and more scientists began to use quantitative methods in their work, Wilson took issue with what he considered their sloppiness in mathematical reasoning. Unfortunately, Pearl became a target of Wilson's watchful eye, and the result was to have a significant impact on applied biology in the United States.

In 1929, Pearl published an article entitled "Cancer and tuberculosis" (PEARL 1929). The article was based on 7500 autopsies conducted at Johns Hopkins, of which 816 had some form of malignancy. Pearl used statistical methods to determine whether tubercular lesions found during these autopsies were correlated with cancer. He found that tubercular lesions occurred more than twice as frequently in the control group as in the group with cancer, suggesting that there is an antagonism between tuberculosis and cancer (WEIR 1993). Wilson took issue with Pearl's analysis on several counts, including the exclusion of leukemia and Hodgkin's disease from the study, as well as Pearl's failure to "distinguish between the quick and the dead" (WEIR 1993). Thus, Pearl may have concluded that tuberculosis and cancer are antagonistic, when in fact early death due to tuberculosis had reduced the chance that cancer would develop at a later age. Wilson, infuriated by what he considered a sloppy use of statistical reasoning, published commentaries on Pearl's paper as well as a research article in 1932, which refuted Pearl's conclusions.

However, the year of Pearl's publication (1929) was to be a crucial turning point for the future of Harvard's Bussey Institution. The Bussey had been a Graduate School of Applied Biology, focusing primarily on genetics and entomology, since its reorganization from an undergraduate school in 1908 (WEIR 1994). In the 20-year period from 1908 to 1928, the Bussey had distinguished itself as one of the foremost genetics research laboratories in the world. This was largely due to the efforts of East and Castle, who trained a generation of students in the new science of genetics; many went on to develop genetics programs at colleges and universities throughout the United States (SAX 1956; NELSON 1993; SNELL and REED 1993; GOLDMAN 2003). In 1927, William M. Wheeler, the Dean of the Bussey, was stepping down from his post. Wheeler and Pearl were both members of the Saturday Night Club of Baltimore and close friends. They, along with the Bussey faculty, had agreed that Pearl would succeed Wheeler as Dean of the Bussey, and this idea was also supported by Harvard's President Lowell. At this time in the Bussey's evolution, there was talk about turning the institution into one that focused on human biology, and Pearl was identified as perhaps

the best person in the world to effect this change. Lowell had offered Pearl the position, and Pearl had accepted. East was initially very pleased with the appointment, writing to Pearl in March of 1929 (WEIR 1993, p. 16):

If anyone in the world can make it (the Bussey Institution) great that man is you. And if the President and Fellows keep their lately aroused interest in biology there ought to be a wonderful future. Naturally the Deanship at the Bussey will be only a stepping stone, and the logical thing will be to make you Director of the whole biological institute.

I am sure that you will find Boston and Cambridge congenial. I have found that the place grows on one with the years. There is only one drawback; good liquor is terribly high—too high for me.

Well! Well! It sure will be nice to grow old together at deah ol Hahvad!

Wilson, hearing of this appointment, wrote a long letter to Wheeler objecting to Pearl's appointment on the grounds that Pearl's mathematical ability was inconsistent with Harvard's standards. The letter was copied to Lowell and the Harvard Cancer Commission, among others (WEIR 1993). For Wilson, Pearl's work on cancer and tuberculosis was the "smoking gun" that showed Pearl's limitations in biostatistical research.

Wilson's protest gathered steam during the summer of 1929, and ultimately a number of former friends and colleagues of Pearl, including East and Castle, became concerned about Pearl's appointment as Dean. Even though Pearl and East had a cordial relationship, and often reviewed each other's work favorably, East may have reacted negatively to Pearl's criticism of the eugenics movement in the United States, of which East was a primary proponent (ANONYMOUS 2002a). On June 18, 1929, Wheeler wrote to Pearl (WEIR 1993, p. 17):

For the past six weeks I have been sick with anxiety over the mess which has been made at Harvard by E. B. Wilson in regard to your appointment. . . . No sooner had Wilson returned from the Academy meetings than he began writing to the president and overseers about you. He has stirred up the whole medical school, the department of economics, and at least four other departments to protest against your coming to Harvard. . . .

Ultimately, even though the Harvard Corporation had decided in favor of Pearl's appointment, it was turned down by the Board of Overseers on a 10 to 9 vote in September 1929 (WEIR 1993). This episode, which came to be known as "The Pearl Affair," is perceived to have been one of the primary forces behind the demise of the Bussey, which took place in 1936 (WEIR 1993).

Despite the pettiness that can at times characterize the process of academic appointments and the resulting damage this can cause, Raymond Pearl's career remains one of tremendous productivity, accomplishment, and insight. Pearl's pioneering work on the relationship be-

tween environment and longevity set the stage for many aspects of modern epidemiology and biostatistics. His many publications in genetics, including both statistical approaches to data analysis and technical aspects of experimentation in genetics, have had great influence. His view of humans as a biological phenomenon was highly influential and was expressed thoughtfully in his posthumously published book *Man the Animal* (PEARL 1946), as well as his “Fundamentalist rogue’s gallery” in the *Quarterly Review*. Finally, his overall scientific output is perhaps unequalled by any scientist of his time. As an example, Pearl founded the *Quarterly Review of Biology* in 1926, and the journal *Human Biology* in 1929. The *Quarterly* was devoted to reviews of recent literature, general articles, lists of new publications. In the first year of the *Quarterly*, Pearl wrote all of the reviews himself. In later years, Pearl did all of the editing himself. Later, his wife assumed much of the work with the *Quarterly Review*, so he could be freed up to work on *Human Biology*.

Pearl received numerous honors, including honorary degrees from The University of Maine, Dartmouth College, and St. John’s College, as well as the Knight of the Crown of Italy, and Honorary Member of the Royal Society of Medicine. He served as President of the American Society of Zoologists, American Society of Naturalists, American Statistical Association, American Association of Physical Anthropologists, and International Union for Scientific Investigation of Population Problems. Pearl died in 1940 at age 61 of coronary thrombosis. His tremendous scientific output and pioneering lines of investigation have stimulated generations of biologists in fields as diverse as agricultural genetics, epidemiology, anthropology, medicine, and human fertility.

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