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FELIX BERNSTEIN and the First Human Marker Locus

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ACCUSTOMED as we now are to thousands of polymorphisms useful as human chromosome markers, it is hard to realize that in the first quarter century of Mendelism there was only one good marker. It is all the more remarkable that its simple mode of inheritance was not understood until the trait had been known for 25 years.

The human blood groups were discovered at the turn of the century (LANDSTEINER 1900), the year of the rediscovery of MENDEL's laws. Two others, MOSS and JANSKY, independently designated the four groups I, II, III and IV. This was fine except that MOSS's I was JANSKY's IV, and vice versa, leading to considerable transfusion confusion in the early days. LANDSTEINER was astute enough to invent a nomenclature that reflected the A and B antigens (and genes), or their absence, and this gradually prevailed–*very* gradually in at least some benighted quarters, for I remember learning about the four groups I, II, III and IV in the 1930s.

It was quickly recognized that the blood groups were inherited and the first plausible hypothesis was put forth by VON DUNGERN and HIRZFELD (1910). Studying 72 families with 102 children, they hypothesized that the A and B antigens were produced by two independent dominant alleles (Table 1). The correct hypothesis of multiple alleles at one locus was not demonstrated until BERNSTEIN did so in 1924 and 1925.

Let O, A, B and AB stand for the proportions of the four types. On the prevailing two-locus hypothesis with Hardy-Weinberg proportions and linkage equilibrium it is clear that the expected frequency of O × AB equals that of A × B, for both are equal to $p_a^2 p_b^2(1 - p_a^2)(1 - p_b^2)$. BERNSTEIN used the equivalent relationship (A + AB)(B + AB) = AB. Applied to the observed proportions in Table 1, the left-hand quantity is (0.500)(0.284) = 0.142, about twice the observed proportion of AB, 0.078.

BERNSTEIN, noting the discrepancy and impressed by the frequency of multiple alleles in Drosophila, tried the single-locus, three-allele hypothesis shown in Table 1. He noted that on this assumption

$$[1 - \sqrt{A + O}] + [1 - \sqrt{B + O}] + \sqrt{O} = p_B + p_A + p_O = 1.$$

As before, this expectation is easily verified by plugging in the expected proportions. Using the observed proportions in Table 1, the three quantities on the left side are 0.154, 0.293, and 0.542, which add up to 0.989.

The agreement with the multiple-allele hypothesis is clearly much closer than with the two-locus model, and BERNSTEIN went on to perform statistical tests. He also found a simple way of estimating the allele frequencies that gave values very close to the maximum likelihood estimates. Instead of following BERNSTEIN's procedures, however, I'll examine the two hypotheses by the methods now widely used for linkage analysis. Following EDWARDS (1992, pp. 39–42), the $\log_e$ likelihood on the two-locus model is −647.5 and on the multiple allele model is −627.5. The difference is 20.0. More familiar to human geneticists is the $\log_{10}$ of the odds (or lod score), which is $(20.0)(\log_{10} e) = 8.7$, so that the likelihood ratio is about 5×10^8, overwhelming support for the multiple-allele alternative.

BERNSTEIN's 1925 paper includes a summary of the already enormous literature of blood group frequencies throughout the world. One population after another showed close agreement with the frequencies expected with three alleles and Hardy-Weinberg proportions. The example in Table 1 is a very small part of the data, a population of Japanese living in Korea.

Why was the earlier incorrect hypothesis so widely accepted from 1910 to 1924? There is a clear difference in the predictions of the two hypotheses when

TABLE 1

Two hypotheses of blood group inheritance

Group	VON DUNGERN and HIRZFELD		BERNSTEIN		Observed proportion
	Genotype	Expected proportion	Genotype	Expected proportion	
O	*aa bb*	$p_a^2\, p_b^2$	*OO*	p_O^2	0.294
A	*A– bb*	$(1 - p_a^2)p_b^2$	*AA, OA*	$p_A^2 + 2p_Op_A$	0.422
B	*aa B–*	$p_a^2\,(1 - p_b^2)$	*BB, OB*	$p_B^2 + 2p_Op_B$	0.206
AB	*A– B–*	$(1 - p_a^2)(1 - p_b^2)$	*AB*	$2p_Ap_B$	0.078
Total		1		1	1.000

The expected proportions assume Hardy-Weinberg ratios and linkage equilibrium. The observed proportions are from 502 Japanese (BERNSTEIN 1925).

one parent is AB. O children may be produced on the two-locus model (if the AB parent is doubly heterozygous), but not on the correct triallelic model. Such children actually were found. In WIENER's (1943) summary of the published data for the years 1924–1932 there were 10 such exceptions among 3205 children. These are now ascribed to errors in typing or misattributed paternity, but were once regarded as supporting the two-locus theory. (Earlier data, when methods were not well established, included a larger fraction of such exceptions.) The ease with which the correct answer was reached, using only population frequencies and simple assumptions, shows the power of BERNSTEIN's population genetic analysis. It is surprising that no one did this earlier, for the Hardy-Weinberg relationship and multiple alleles had been well known for a decade. I suspect that World War I was one cause.

FELIX BERNSTEIN, 1878–1956: FELIX BERNSTEIN was remarkable for his originality, his wide ranging interests, and his skills in both pure and applied mathematics. His grandfather, ARON BERNSTEIN (1812–1884), was a well known and multi-talented writer on, among other things, science and politics. When ALBERT EINSTEIN was a young man he was given one of BERNSTEIN's science books and became so fascinated that he gave up the idea of becoming a violinist in favor of science. If the stories about EINSTEIN's fiddle playing are correct, this was a salutary decision for both physics and music.

FELIX BERNSTEIN was born on February 24, 1878, in Halle, Germany, and spent his childhood and youth there. He was given the name FELIX because his mother, who composed music and was an accomplished pianist, hoped he would be a musician and named him after FELIX MENDELSSOHN. Music, however, was about the only field in which he did not become interested. His artistic love was painting and sculpture.

BERNSTEIN's becoming a mathematician is a fascinating story involving an improbable and fortunate coincidence. His father, JULIUS BERNSTEIN, was a friend of the mathematician GEORG CANTOR, and FELIX, while still in gymnasium in Halle, attended CANTOR's seminar. It was his good fortune to be introduced to set theory before the subject became popular.

FELIX BERNSTEIN (1933)

In 1896 CANTOR took a holiday and left some proofs that young BERNSTEIN had volunteered to correct. As he was correcting the proofs, BERNSTEIN (while shaving, the story goes) thought of a proof of a theorem that CANTOR had been wrestling with and had been unable to prove to his satisfaction (NATHAN 1981). This "equivalence theorem of two sets" states that if

each of two sets, A and B, is equivalent to a subset of the other, then A is equivalent to B. This has become a central theorem of set theory, first proved by this 18-year-old. For a contemporary discussion and proof, see STOLL (1963, p. 80*ff*). CANTOR was much impressed by the proof and communicated it to BOREL for the First International Mathematical Congress in Zurich. Meanwhile, BERNSTEIN, having finished his schooling in Halle, became a student of fine arts in Pisa, where he studied philosophy, archeology, and art history. His sister was an artist and studied with MATISSE. While he was at Pisa, two mathematicians there who had heard CANTOR discussing the equivalence theorem, persuaded the young BERNSTEIN to become a mathematician. He then went to Göttingen, where he was one of HILBERT's first doctorates and received his degree in 1901. He had a distinguished career in mathematics and showed his versatility by writing on a wide variety of mathematical topics. He retained his interest in art, though, spent many hours in museums and galleries, and entertained his family and friends by constructing statues of modeling clay.

He also had an interest in applied mathematics. After some years in Halle, he was appointed to Göttingen as Associate Professor of Mathematical Statistics in 1911. From 1921 to 1933 he was director of the Institute of Mathematical Statistics. After World War I he was head of the statistical branch of the office of rationing and in 1921 became Commissioner of Finance.

In 1928 BERNSTEIN came to the United States to work on epidemiology at Harvard, and during the next few years he had several visiting positions. In 1933 and 1934, having been dismissed from his position at Göttingen, he brought his family to this country. For a while he was guest professor at Columbia University. The anthropologist, FRANZ BOAS, had obtained a grant to support him for a year, with the understanding that Columbia would then hire him permanently. But Columbia never made good on this verbal commitment, and for the year 1945–1946 he was left without support. This elicited a comment from his friend, R. A. FISHER: "But Bernstein, why did you not come to England. In England, a handshake from a gentleman is as good as a signed contract." (Later, in 1954, FISHER happily wrote to inform BERNSTEIN of his election as an honorary fellow of the Royal Statistical Society.) From 1946 to 1949 he taught mathematics at Triple Cities College, now part of SUNY-Binghamton. On the hundredth anniversary of his birth, in 1978, the Department of Mathematical Sciences there announced the "Felix Bernstein Teaching Assistantship" in honor of this "pioneer in the development of mathematical set theory . . . and world renowned statistician and pioneer in the field of population genetics." He eventually returned to Europe, spending time in Göttingen, Rome, and Freiburg, and died in Zurich on December 3, 1956.

The biography by FREWER (1981) lists 128 articles on an astonishing variety of subjects, including mathematics (set theory, convex functions, the Laplace transform, number theory, differential equations, Fermat's last theorem, the Fourier integral, mathematical statistics), economics, anthropology, tuberculosis therapy, human life span, assessing aging from eye lens refraction, polio, age and cancer, and, of course, genetics.

BERNSTEIN was a long-time close friend of EINSTEIN, starting in the 1910s in Germany and continuing throughout their lives (which ended at about the same time). Because of his involvement in pensions and insurance in Germany, he promoted attempts to establish unemployment insurance in the United States. He and Einstein also found positions for displaced European scholars in the 1930s.

Other contributions to genetics: BERNSTEIN's interest in genetics, if we can judge from his publications, began in the early 1920s. An early study (BERNSTEIN 1922a) involved the analysis of multiple factors in quantitative traits. In the same year (1922b) he published an amusing theory for inheritance of voice range, the first suggestion of inheritance of a sex-influenced character in man. He hypothesized a reverse sex-dependence such that bass and soprano represent one homozygous type, tenor and alto the other, and baritones and mezzo-soprano the heterozygotes. This idea has now been forgotten but I remember hearing it as a student.

BERNSTEIN's major contribution was blood group inheritance and he wrote extensively on this subject. Having found a marker, he naturally become interested in using it for linkage studies, and invented a way to get around the problem that in man the linkage phase is usually not known. For example, in a series of sibships from the mating $Aa\ Bb \times aa\ bb$, how do we measure recombination when the recombinant phenotypes under one linkage phase are the nonrecombinants with the other? BERNSTEIN (1931a) cleverly invented the statistic $y = (Aa\ Bb + aa\ bb)(Aa\ bb + aa\ Bb)$, the value of which depends on the degree of linkage but not on the linkage phase (nor does it require that the linkage phases be equally frequent). He prepared a series of tables of the expected value of y for different values of the recombination fraction and sibship size, with which the data could be compared. This method has been superseded by a series of advances starting with FISHER and leading to current computer-dependent likelihood ratio methods.

BERNSTEIN (1930) also considered the effects of consanguinity on Hardy-Weinberg expectations, particularly in the blood groups. His α is equivalent to WRIGHT's F. He discussed, as others did, the approach

to linkage equilibrium under random mating.

He was the first to apply a mixture formula to determine the ancestry of racially mixed populations. If q_1, q_2 and q_m are the allele frequencies in the two parental populations and the mixed group, then the proportional contribution of the first population to the mixture is $M = (q_m - q_1)/(q_2 - q_1)$. This simple formula has been widely applied.

One of his major developments was a method of correcting for ascertainment bias in testing Mendelian ratios. When, for example, parents heterozygous for a recessive disease are ascertained through affected children, those heterozygous parents who happen to have no affected children are missed and the Mendelian ratio is distorted. BERNSTEIN worked out a procedure for correcting this error and testing the significance of the departure from Mendelian expectations when such a correction is made. This was presented as an alternative and compared to WEINBERG's sib method (BERNSTEIN 1931b). Better procedures were later developed by HALDANE, FISHER, MORTON, and others, so BERNSTEIN's work is now mainly of historical interest.

BERNSTEIN and WEINBERG were the two leaders in developing techniques for human genetic study, not only in Germany but throughout the world. The contrast in their backgrounds is striking. Both had other interests. While BERNSTEIN was a mathematician, WEINBERG was a busy obstetrician who somehow found time to think about human genetics. Yet each in his own way had a knack for finding ways to solve problems that are trivially easy in experimental plants and animals, but that called for a touch of genius in that genetically refractory species, *Homo sapiens*. This, of course, was long before molecular markers, computers, and CEPH families made things easier.

Final remark: I hope that someone will take advantage of BERNSTEIN's abundant published record to do a much more thorough study of this multifaceted man. His professional and personal relations with WEINBERG should be of great interest. Among other things, his correspondence with EINSTEIN, located at Boston University, is a gold mine.

FELIX BERNSTEIN, like so many German Jewish scientists, had his career disrupted by Nazi politics. Undoubtedly his life would have been quite different had history taken a different course and had he been able to spend his life in the cultural environment that Göttingen supplied before the 1930s. As judged by number of published papers, his research productivity decreased greatly after his move to the United States. I suspect that this was caused, at least partially, by the necessity of moving from one temporary position to another. And, as I said, he spent a great deal of effort, often in collaboration with EINSTEIN, in social causes and in finding positions for other displaced European scientists. In one poignant note he asked that his name not be revealed in this context to protect his relatives still in Germany. Alas, they perished anyhow.

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