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Going on an Antedate

A strange history of imperfect perfect proportions.

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In the mid-1700s, the English language was rather out of control. In the absence of a satisfactory reference, word meanings were unclear. Even Shakespeare had already become somewhat obscure to most readers. So the intellectual-about-town, Samuel Johnson, convinced investors that an English dictionary based on improved principles would be commercially successful.[1–3] Existing dictionaries were based on "a genealogy of sentiments," as author had copied author over time. Instead, Johnson argued for an approach that reflected "intellectual history," a term he appears to have coined (Fig. 1). Appearing in 1755, "Johnson's" became the standard dictionary for about a century. He showed a word's evolving meaning by using historical examples of its usage.

In science as well as literature, meaning can become blurred over time. Perhaps even more problematic and harder to trace than word definitions are changes in concepts. An interesting example is the Hardy-Weinberg principle (HW). After teaching the essentials of Darwinian evolution, Mendelian inheritance, molecular biology, and speciation, students are routinely introduced to HW. We teach it as a stable genetic baseline, the HW equilibrium, deviation from which leads to the changes that define evolution. However, since it will be on the test, many students (even those who are awake) see HW only as an algebraic threat to their grade-point average. As one student griped, "Let me get this straight. When nothing happens . . . nothing changes? Duh."

Over decades of textbooks, HW appears to be taught largely because it always has been taught. It's part of our pedagogic heritage, but its meaning and rationale have become hidden in the dusty volumes of past journal articles. It seems unthinkable to omit it. But why? To see that, we have to go back to the origin of modern genetics.

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FIRST PRINCIPLES FIRST

When Gregor Mendel did his famous experiments with peas, the nature of inheritance was unknown. Following an ancient idea, Darwin thought that each organ transmitted a tiny miniature of itself to the gonads and that the "gemmules" from each parent blended to form the offspring. It was quickly shown that blending didn't work, but Darwin's cousin Francis Galton advanced a modified theory of Ancestral Heredity: You receive a set of heritable units from your parents. The fertilized egg uses up half of that material to construct you as an organism; the remaining half is saved to be doled out to your children, who get half their material from you and half from your spouse. Thus, your direct contribution is cut by half in each succeeding generation, gradually petering out until there is hardly any left. This "biometric" theory explained the inheritance patterns of quantitative traits like skin color.

Mendel's ideas were different. He was trained to think that organic nature follows the same laws as does the physical world of fundamental particles.[4–6] Inheritance must follow mathematical rules. He used hybridization experiments to deduce those rules from the relative frequency of alternative traits such as green versus yellow peas. He succeeded because he deliberately chose traits known to breed true in different strains of peas, and he showed that the rules were general by repeating his experiments and testing seven unrelated traits.

Mendel avoided traits with blurry intermediates, but he did explain a fact that also puzzled Darwin and Galton. A trait could disappear in one generation, then reappear in the next. If yellow and green peas were crossed, for example, all the offspring plants bore yellow peas. But if he then crossed those plants, the green trait would reappear in the next generation and—a vital clue—the proportions of the two types were predictable and repeatable. In particular, in the offspring cross he found his famous 3:1 ratio that always favored one trait. He inferred that a plant inherited nonblending factors from each parent, and was equally likely to transmit either to its offspring. In modern terms, if a yellow-producing allele (variant state) **A** is dominant over the green **a,** the original **AA** × **aa** (yellow × green) cross produces only yellow **Aa** offspring. Listing the maternally derived allele first, when you cross these with each other, you get equal numbers of **AA, aA, Aa,** and **aa**

I have ſometimes, though rarely, yielded to the temptation of exhibiting a genealogy of ſentiments, by ſhewing how one authour copied the thoughts and diction of another: ſuch quotations are indeed little more than repetitions, which might juſtly be cenſured, did they not gratify the mind, by affording a kind of intellectual hiſtory.

Figure 1. Some defining wisdom from Samuel Johnson's Preface, 1755.[1]

offspring. Since only the **aa**s are green, that is Mendel's famous 3:1 ratio.

TODAY'S STUDENTS NOT THE ONLY ONES CONFUSED

Mendel's work was recognized in 1900, and "gene" was coined by the Danish botanist Wilhelm Johannssen in 1909 to refer to his inherited particles, whatever they are. As Samuel Johnson might find amusing, so many new functional aspects of the genome have been found that the definition has morphed to its latest hardly-helpful incarnation of "a union of genomic sequences encoding a coherent set of potentially overlapping functional products."[7]

When we teach old, established, everybody-knows-that concepts, it's easy to forget that a century ago these were new ideas that solved real scientific conundrums, and in ways that were not always evident at the time.

Mendel's 3:1 ratio refers to a single generation of peas from a breeding experiment. But if this is a general law of inheritance, what would happen over many generations—on the evolutionary scale? This proved to be a surprisingly confusing question in which evolution, semantics, and the myopic eye of preconception entered the drama. The effect of a genotype on producing a trait was confused with its effect on the competitive fitness of the trait. Perhaps, in part, Mendel's word "dominirende," or "dominating," suggested a trait's ability to bully its way to selective victory.[4,8] Only later did the translation become "dominant" and thereby lose any such evolutionary connotation. Johnson would be pleased. Two other concepts were confused, the descriptive word "proportion" and the action-related word "probability," which still are often confused today.

In 1902, the English statistician George Udny Yule asked what would happen to Mendelian proportions if you hybridized two strains (**AA** × **aa**) and let their descendants randomly breed thereafter instead of setting up controlled breeding for each generation. Yule correctly inferred that under Mendel's rules the classic 3:1 ratio would persist in every future generation. Since the founders in Yule's thought-experiment were **AA** and **aa,** hence the allele frequencies were 0.5, this evolutionary result was a not terribly surprising extension of Mendel's own experiments. But Yule then asked what would happen if only the dominant 75% of the population, rather than everybody, were allowed to breed? This would be the kind of artificial selection that agricultural breeders had done for centuries, and Darwin used as a model for evolution by natural selection. Yule wrongly calculated that in a few generations the dominants would approach a limiting proportion of 85.355339%. This seemed to show that Galton's theory was right: The wimpy recessive trait may stay around, but diluted. But Mendel was right, too, because the recessive keeps reappearing. Yule concluded that Mendel's principles were a special case of ancestral heredity for a dominant trait.

However, W. E. Castle, the leading American defender of Mendel's theory, was delighted to find a mistake in Yule's calculation; a realization showed the failure of Galton's theory. If selection consistently eliminated the recessive every generation, but all possible matings among the remaining dominants are calculated, the dominant will very, very, very slowly approach 100%. There is no stable proportion of recessives with constant selection against them. Nonetheless, Castle showed that once selective breeding against recessives stops, the then-current ratio of dominants to recessives, whatever it is, will remain indefinitely. So depending on when selective breeding stops, there are any number of possible stable proportions. Independently, in England, Karl Pearson proved that the 3:1 ratio is stable in a random-mating population. But, like Yule, he started with equal allele frequencies and never generalized these results to all possible frequencies. The great statistician should have done that, but he didn't.

By 1908, confusion was rampant. A well-known Mendelian, Reginald Punnett, presented a paper on Mendelism in humans, citing eye color and brachydactyly (short fingers) as examples, which puzzled Yule. In a random-mating population like England, why didn't Punnett find a 3:1 ratio of brown to blue eyes? Now it was Punnett's turn to be puzzled, due to his inaccurate reading of some comments published by Yule. Why did Yule think that Punnett thought that the population should increasingly be brown-eyed and brachydactylous? After all, whether brown eyes or short fingers were increasing or not, their inheritance pattern was clearly Mendelian!

By this time, the relationship among variation, heredity, breeding, selection, and evolution had been mixed into a heady brew of conceptual confusion of heroic proportions. Four people, Yule, Castle, Pearson, and Punnett (Fig. 2) had independently seen what the problem was, but each had solved only part of it. But what has all this to do with Hardy and Weinberg, whoever they were?

HARDY, WEINBERG, AND THEIR SILENT PARTNERS

Punnett was confused, but smart enough to know that he wasn't smart enough to solve the questions: How

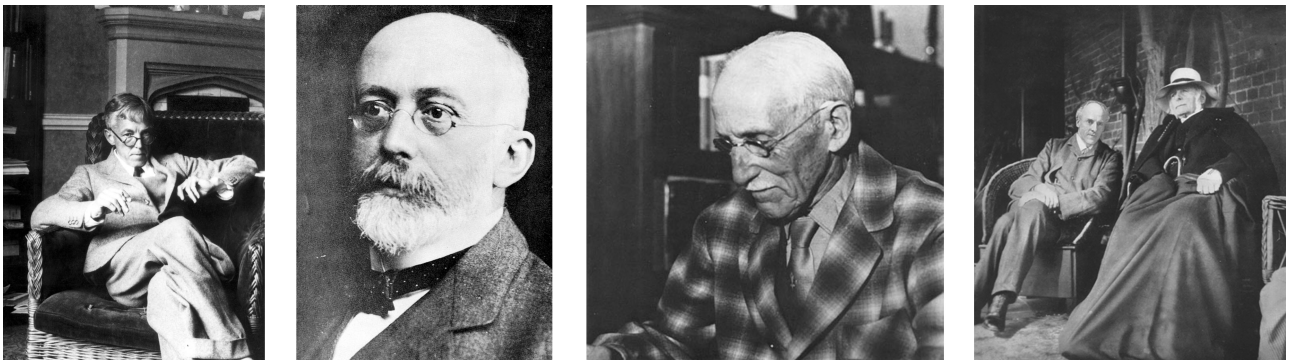

Figure 2. Hardy, Weinberg, and Castle equilibrate. About Hardy's picture, it was said that anyone sitting like that had to have been educated at a public school.[9] A. Hardy, B. Weinberg, C. Castle (Sources: Master and Fellows of Trinity College, Cambridge; Weinberg[10]; Castle, Jackson National Laboratory.) D. Pearson with the 87-year old Galton (www.galton.org).

does Mendelian inheritance affect the course of evolution? What would happen in a population that did not have equal allele frequencies? He sought help from his Cambridge friend and cricket partner, the famous mathematician G. H. Hardy.

In a terse but coyly worded letter to *Science*, Hardy pointed out that if parents are chosen at random so that all types are represented in their proportions in the population, rather than by selectively breeding only certain parental combinations, then in the very next generation the population will attain stable genotype proportions, no matter what the starting frequency. Here's how to see this easily. In a given mating between two parent types, one only has to deal with the specific offspring they can produce. Since Mendel's law says that each parent has a probability of 1/2 of transmitting either of its two alleles, the offspring proportions are simple to work out, as we saw earlier with Mendel's 3:1 in **Aa** × **Aa** matings.

In offspring produced by a *population* of parents, the probabilities are not 1/2, but depend on the allele frequencies; that is, their proportions in the population. If parents are mating at random, these proportions are the probabilities that an allele in a randomly sampled offspring is of that type. If a gene has two alleles, with proportions p and q in the population, the probability that the offspring will be an **AA** homozygote is the probability of drawing an A and then doing it again: $p \cdot p = p^2$; the probability it's **aa** is q^2. An **Aa** heterozygote is produced by drawing an **A** the first time, then **a,** or vice versa: $pq + qp$ equals $2pq$. These are the famous HW proportions, the bane of medical-school aspirants. Rather than thinking of drawing random pairs of alleles from a parental gene pool, you can achieve the same result by enumerating the offspring of all possible matings, **AA** × **AA, Aa** × **aa,** and so forth, in their respective proportions in the population. (We usually don't make students do that.) The HW *genotype* proportions hold whether or not there's any dominance, but if there is, in the classic **Aa** × **Aa** mating, $p = 1/2$, and you get Mendel's 3:1 *trait* ratio.

The German physician and self-taught geneticist Wilhelm Weinberg was searching for a human Mendelian factor to study. His clinical observations suggested that Mendel's principles might apply to humans as well as peas, and he thought dizygotic twinning might be a likely candidate. Weinberg worked out the tedious algebra for all possible matings of parents who might produce twins, implicitly assuming random mating. He found that the proportion of the genotypes would stabilize after the first generation, making it possible to predict the frequency of twins among a given offspring cohort. To his satisfaction, twin phenotypes did behave as a Mendelian recessive. Perhaps because he wrote in German, used what were for most biologists sophisticated mathematics, and had severely criticized Pearson's biometrics, Weinberg was summarily ignored. Although his paper preceded Hardy's 1908 paper by about six weeks, he was not appreciated until 1943. But, in many ways, it was he who laid the foundations of modern population genetics.

The HW principle resolved a host of conundrums. It showed how variation, heredity, mutation, natural selection, selective breeding, random mating, and Mendelian ratios are different but related aspects of the evolutionary process. The 3:1 trait ratio played a major role in the history of this understanding. It has no special status in nature, but it can seem to if Mendelian experimental crosses are mistaken for natural populations. As Castle had realized, any allele frequency generates stable genotype proportions once breeders stop selective favoring of a given genotype and allow random mating.

Mendelian heredity by itself does not change the frequency of variation and has no direct effect on evolution. Dominant alleles are not necessarily dominating in fitness. Nature is free to choose. But the stable HW proportions, called Hardy-Weinberg equilibrium, were seen as an idealized baseline against which to evaluate the effect of the Four Forcemen of the Evolutionary Apocalypse: mutation, selection, migration, and chance (genetic drift). Since each of these changes allele frequencies, the search for HW proportions became a veritable growth industry in the 1960s and 1970s as anthropologists collected biological samples from indigenous

people and estimated allele frequencies for the MN, ABO, and many other genes. But this is generally ivory tower pedagogy because, ironically, HW is not very useful for studying evolution out there where it really happens.

POPULATIONS EVOLVING . . . OR NOT

Ironically, though HW is held to reflect nonevolution, and HW proportions are usually found in nature, evolution does happen. That seems like a contradiction until we look closely. First, every population is finite, which means that allele frequencies essentially always change. For example, the parents of a population of 55 individuals with allele frequency of 0.5 would be expected to produce 1/4 **AA**s, but there can't actually be 13.75 people, even if everybody is mating at random. The offspring frequency will not be exactly 0.5. There are many other ways by which purely chance aspects of life and death change allele frequencies. This is genetic drift. Even Mendel knew you had to do many substantial experiments to reveal the theoretical proportions, which are never found exactly. Unlike controlled breeding, evolution is not a repeatable experiment. There's no starting over each generation, a fact Hardy recognized.[11] Even tiny differences add up over millions of years.

Mutation changes allele frequencies, but is so rare that we can hardly ever collect samples large enough to detect its effect on HW proportions. Migration brings new variation into a population. But until recently, that's mainly been by mate exchange among nearby villages, which tend to be populated by close relatives with similar allele frequencies, so migration is usually just another aspect of genetic drift.

But at least there is natural selection, no? Usually, no! As Darwin stressed, and most research has shown, natural selection is generally very slow. Consequently, most selective differences among genotypes are so small that it has proven very difficult to detect selection by deviation from HW proportions. Most of the exceptions are of very fast and strong selection, like pesticide resistance. Also, confusion of definition between strong, intentional experimental selection and weak, blind natural selection played a role in our HW history. Authors might know what they have in mind, but illustrating that by brief quotes could confuse a lexicographer like Johnson. But as a rule, drift is a much greater factor that obscures most of the direct evidence of selection in nature.

What this means is that the Four Forcemen of Evolution may be riding all the time, but deviation from HW is not a good way to find them. Decades of testing in real human populations have shown that most loci are in HW. Actually, things are rarely in exact HW. What we really mean when we say a population or sample is "in HW" is that genotype proportions differ from HW by so little that, based on standard statistical significance criteria the deviations aren't big enough for us to allege that anything nonrandom is going on, even if it is.

Convenient as they are as a baseline for teaching how evolution works, in fact HW proportions are not even necessary for the forces of evolution to occur! Nonrandom mating, such as assortative mating in which like mates with like, can lead to deviations from HW (more homozygotes). But selection, mutation, migration, and drift still occur. HW affects the relative frequency with which a given trait is presented to nature for screening to occur, but is not required for that screening. Yet even if, in practice, HW is an elusive baseline for detecting evolution, it is nevertheless very useful in many other ways that are not as well known.

DESPITE EVERY WAKING MOMENT'S OBSESSION

Students not too tied up in its algebra should ask why HW proportions are so widely found in nature. After all, students complain about the algebra mainly because it keeps them from what really occupies their every waking moment: choosing who to mate with. Only a few would acknowledge that they mate at random, or at least try to. Since, behaviorally, mating is anything but random, HW proportions seem paradoxical. The key is random mating with respect to what? The traits that determine mate choice involve only a tiny fraction of an individual's genes. The rest are effectively combining at random. This may change, of course, when DNA-testing chips make it possible to check out your date's entire genome.

If an allele affects one's risk of a chronic disease, then genotypes containing that allele may die off faster with age than other genotypes. This is the case with Alzheimer's disease and the gene called APOE. Carriers of the **e4** allele at this gene preferentially die at younger ages, so the genotype frequencies change noticeably as a cohort gets older. This is evidence of survival selection against the gene's effects. But since the effects are postreproductive, the resulting deviation from HW with age may have nothing to do with evolutionary selection.

If genes affect a disease risk, such as of deafness or diabetes, persons with the disease socialize and may be more likely to marry. That is assortative mating and can lead to a deviation from HW proportions at the responsible genes, which can be important in studies designed to identify those genes, because the statistical methods typically assume HW.

Methods for inferring peoples' ancestry or for identifying genes associated with disease can be substantially affected if the population has social structure related to genes, as might occur with ethnic subdivision among people with different historical ancestry. Population structure introduces deviations from HW proportions in an overall sample, even if there is random mating within each subdivision. The result, called the Wahlund effect, is an apparent excess of homozygotes compared to what would be expected from the overall allele frequency in the population. This deviation can lead to false identification of genes that, in fact, have nothing to do with a trait under study, so it is important to test for it.

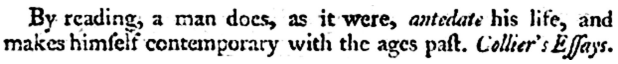
By reading, a man does, as it were, *antedate* his life, and makes himself contemporary with the ages past. *Collier's Essays.*

Figure 3. Johnson defines ''antedate'' by quoting from an essay by his contemporary Jeremy Collier.

HW applies to association among alleles at different genes, as well as those at the same gene. When genes are located close together on the same chromosome, nonrandom association among their alleles, called linkage disequilibrium, can be a useful indicator of a history of natural selection affecting that chromosome region. For a given gene, random mating generates HW within a single generation due to the Mendelian principle called segregation. But alleles at different genes along a chromosome become associated due to their shared history, which can reflect hundreds of generations, even when there is random mating, because the alleles do not follow the Mendelian principle called independent assortment except by the process of recombination. Linkage disequilibrium is a potentially strong, if indirect, indicator of recent natural selection, because favoring one spot on a chromosome for functional reasons also favors the nearby genes by "hitchhiking." This is a powerful tool for gene mapping, where we can use known polymorphic sites on a chromosome to help find unsuspected nearby sites causally associated with a trait we're interested in.

One of the most important sources of deviation from HW proportions has nothing to do with the people being studied. It has to do with laboratory error and takes advantage of the fact that, for most genes, human populations do not significantly deviate from HW. When a genotype is determined, the chemical reaction (DNA sequence) has to detect both alleles with equal effectiveness. In heterozygotes, that means both reactions have to work. For example, if **A** reaction fails, an **Aa** person will appear to be an **aa** genotype. So a standard test in genetic studies is to look for HW, regardless of any thoughts we may have about mating pattern.

ANTEDATING OURSELVES

Reading beyond narrow technical confines has become something of a lost art. But it's a confining loss that leaves us vulnerable to semantic or cultural traps. For example, even today students routinely slip into thinking that alleles in nature have equal frequency. Why? Because of the sometimes reflexive confusion of Mendelian breeding experiments and evolution: **Aa** × **Aa** matings have classical 3:1 offspring ratios that illustrate dominance, while matings like **AA** × **aa** are less pedagogically useful because they only produce one kind of offspring. In fact, most alleles, at most genes, in most populations, have frequencies far from 1/2.

The search for general properties of inheritance and their relation to evolution was pursued largely in the dark, or in selected corners of light. Darwin knew of traits that "refused to blend," and Mendel intentionally avoided traits that did. Darwin knew that some traits showed "prepotency" (dominance) of one state over another in hybrids.[15] He was aware of many of the aspects of segregation that Mendel formally quantified. Darwin had materials in his library that scantily referred to Mendel's findings (but not a copy of Mendel's actual paper), yet either didn't know it or ignored them.[16] Groping in the dark for an explanation of inheritance, those were not the dots he connected.

Mendel was a brilliant inductive experimentalist and deductive theoretician.[5] He ignored inconvenient traits, focusing on traits that bred true to find a theoretical basis for using hybridization to improve horticultural stocks. He experimented with equal frequency of the factors (alleles) in which he was interested, and in a cross there are only two. He would have had a hard time drawing his conclusions had he tried to work with wild peas in natural proportions, with many alleles of varying frequencies, while Darwin extrapolated from breeding to understand evolution in the wild, where he felt the important traits were continuous, not discrete.

Samuel Johnson illustrated the meaning of the word "antedate" with this quote: 'By reading, a man does, as it were, antedate his life, and makes himself contemporary with the ages past"[1] (Fig. 3). Intellectual history is not valuable just for historians or old fogies nostalgic for simpler days. To antedate ourselves and become contemporaries with our predecessors is to see what they said and why. They were as intelligent as we are, and had good reasons for what they said.

The formal basis of evolutionary theory is often explained in relation to HW proportions. The point of force-marching students through it is so they can understand why nothing happens when nothing happens. We less often point out that in studying evolution in the real world, where something *always* happens, we struggle to determine which of the many possible ways to generate small differences from ideal expectations is actually responsible for evolution. HW is useful in other important ways, not least being its historic role en route to understanding the subtle connection between inheritance and evolution. It is a simple principle that turned out not to be so simple after all.

NOTES

We welcome comments on this column: kenweiss@psu.edu. There is a feedback and supplemental material page at http://www.anthro.psu.edu/weiss lab/index.html. We thank Anne Buchanan, Heather Lawson, and John Fleagle for critically reading this manuscript.

REFERENCES

1 Johnson S. 1755. Dictionary of the English language. London: Strahan & Others.

2 Hitchings H. 2006. Defining the world: The extraordinary story of Johnson's dictionary. New York: Picador.

3 Boswell J. 1791. The life of Samuel Johnson, LL.D: comprehending an account of his studies

and numerous works . . . In two volumes. London: printed by Henry Baldwin, for Charles Dilly.

4 Corcos AG, Monaghan FV, editors. 1993. Gregor Mendel's experiments on plant hybrids: a guided study. New Brunswick, NJ: Rutgers University Press.

5 Orel V. 1996. Gregor Mendel: the first geneticist. Oxford: Oxford University Press.

6 Weiss KM. 2002. Goings on in Mendel's garden. Evol Anthropol 11:40–44.

7 Gerstein MB, Bruce C, Rozowsky JS, Zheng D, Du J, Korbel JO, Emanuelsson O, Zhang ZD, Weissman S, Snyder M. 2007. What is a gene, post-ENCODE? History and updated definition. Genome Res 17:669–681.

8 Sturtevant AH. 1965. A history of genetics. New York: Harper and Row.

9 Kanigel R. 1991. The man who knew infinity: a life of the genius Ramanujan. New York: Washington Square Press.

10 Stern C. 1962. Wilhelm Weinberg. Genetics 47:1–5.

11 Hardy GH. 1908. Mendelian Proportions in a mixed population. Science 28:49–50.

12 Weinberg W. 1908. Über den Nachweis der Vererbung beim Menschen. Jahreshefte des Vereins für vaterländische Naturkunde in Württemberg 64:368–382.

13 Boyer SH, editor. 1963. Papers on human genetics. Englewood Cliffs: Prentice-Hall.

14 Castle WE. 1903. The laws of Galton and Mendel and some laws governing race improvement by selection. Proc Am Acad Sci 35:233–242.

15 Darwin C. 1900. The variation of animals and plants under domestication (orig. pub. 1868). New York: D. Appleton.

16 Sclater A. 2003. The exent of Charles Darwin's knowledge of Mendel. Georgia J Sci 61:134–137.

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