Perspectives

Anecdotal, Historical and Critical Commentaries on Genetics

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G. H. Hardy (1908) and Hardy–Weinberg Equilibrium

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More attention to the History of Science is needed, as much by scientists as by historians, and especially by biologists, and this should mean a deliberate attempt to understand the thoughts of the great masters of the past, to see in what circumstances or intellectual *milieu* their ideas were formed, where they took the wrong turning or stopped short on the right track.

Fisher 1959, pp. 16–17

On closer examination, however, the hope of finding a "first" comes to grief because of the historically dynamic character of ideas. If we describe a result with sufficient vagueness, there seems to be an endless sequence of those who had something within the vague specifications. Even plagiarists usually introduce innovations! If we specify the idea or result precisely, it turns out that exact duplications seldom occur, so that every mathematical event is a "first", and the priority question becomes trivial.

May 1975, pp. 315–317

ALTHOUGH this is an account of G. H. Hardy's role in establishing the existence of what is now known as "Hardy–Weinberg equilbrium," we start with Weinberg's description of the problem and its solution, which cannot be bettered. To do so is also to recognize that his solution in fact preceded Hardy's (which was obtained independently).

On January 13, 1908, Wilhelm Weinberg read to an evening meeting in Stuttgart, Germany, a paper in which he "derived the general equilibrium principle for a single locus with two alleles" (Weinberg 1908; Provine 1971; English translations in Boyer 1963; Jameson 1977). Mendel (1866) had already initiated population genetics by considering the consequences of continued selfing starting with the cross $Aa \times Aa$, obtaining 1 AA: 2 Aa: 1 aa in the first generation and

$$2^n - 1\,AA:\ 2\,Aa:\ 2^n - 1\,aa$$

in the nth (assuming for simplicity that each plant produced four seeds). With A dominant to a as usual this gives phenotypic proportions $2^n + 1$ "A": $2^n - 1$ "a" as noted by Weinberg [although Mendel's nth generation was his $(n - 1)$th]. He did not explicitly refer to Mendel, but he was surely familiar with Mendel's paper. He went on, "This situation appears much different when Mendelian inheritance is viewed under the influence of panmixia" (Weinberg 1908) and, starting with arbitrary proportions m and n (not the same n as before; $m + n = 1$) of each of the two homozygotes AA and aa, he obtained "by application of the symbolism of the binomial theorem" the daughter generation

$$m^2 AA + 2mnAa + n^2 aa.$$

Another generation of random mating led by direct calculation to the same proportions among the offspring and "We thus obtain the same distribution of pure types and hybrids for each generation under panmixia" (Weinberg 1908). Weinberg then uses his result to work out the numbers of the two phenotypes to be expected among the relatives of an individual of known phenotype, but this does not now concern us. Rather, he has established the "Hardy–Weinberg law" in the most obvious and direct manner.

Meanwhile in England, between the rediscovery of Mendel's paper in 1900 and the publication by the mathematician G. H. Hardy of the same result as Weinberg's in July 1908 in the American weekly Science (Hardy 1908), confusion reigned. The animosity between Karl Pearson's "biometricians" and William Bateson's "Mendelians" had so clouded the atmosphere that not until Bateson's lieutenant R. C. Punnett appealed to his mathematical friend G. H. Hardy was Weinberg's simple law independently derived.

The story of how Britain's foremost mathematician became involved in a simple problem of Mendelian

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genetics has been told many times, often with embellishments. Many years later Punnett gave his own account in a lecture (Punnett 1950). Provine (1971) has given an account of the surrounding events leading up to Hardy's Science letter, and Bulmer (2003) a slightly fuller one. Yet there is still more to be said, in particular how the lack of understanding between the biometricians and the Mendelians delayed the solution to a problem that, if both parties had paid more attention to Mendel's paper itself, should never have arisen.

Roughly speaking, Punnett's concern was why in a random-mating population the dominants did not in the course of time drive out the recessives. The answer is immediate from Mendel's first law. Segregation is independent of the segregants. Dominance has nothing to do with it. Neither has random mating. Mendel's own example of selfing had already shown this clearly. For it is an immediate consequence of Mendel's law of segregation that the expected frequencies of the genes among the offspring of two parents are equal to the frequencies of those genes in the parents themselves. Provided therefore that each mating is equally fertile and that the two groups of mating individuals, male and female, are both representative of the population at large in respect to their gene frequencies, no change in gene frequency from one generation to the next will take place, even in the presence of assortative mating. Ironically, therefore, the actual problem that led Hardy to assume random mating among genotypes and thereby derive the Hardy–Weinberg law was not a genotypic problem at all.

YULE AND PEARSON

G. Udny Yule began his association with Karl Pearson in 1893, and in 1902 he published a long paper in two parts that starts with a tirade against Bateson for the colorful language of his writings on Mendelism ["one cannot help feeling that his speculations would have had more value had he kept his emotions under better control; the style and method of the religious revivalist are ill-suited to scientific controversy" (Yule 1902)]. Only after a lengthy discussion of the law of ancestral heredity does Yule settle down, in part II, to a consideration of "Mendel's laws." He first summarizes Mendel's results and conclusions and then considers their relevance to "intraracial heredity":

> The first question to be asked in such a discussion, is one that does not seem to have occurred to any of Mendel's followers, *viz.*: what, exactly, happens if the two races A and a are left to themselves to inter-cross freely *as if they were one race?* . . . Now when [homozygous] A's and a's are first inter-crossed we get the series of *uniform* hybrids [Aa]; when these are inter-bred we get the series of three dominant forms (two hybrids, one pure) to one recessive. If all these are again intercrossed at random the composition remains unaltered. "Dominant" [A] and "recessive" [a] gametes are equally frequent, and consequently conjugation of a "dominant" gamete [A] will take place with a "recessive" [a] as frequently as with another "dominant" gamete (Yule 1902).

Here is Hardy–Weinberg clearly established for a gene frequency of one-half. But Yule immediately diverts to calculating the proportion of dominant offspring from a dominant parent (as Weinberg was to do later for arbitrary gene frequencies) because he wants to relate Mendel's results to the law of ancestral heredity, and he does not comment further on his demonstration that the gene frequencies remain unchanged under random mating. Yule's introduction of the concept of random mating itself was a notable contribution to Mendelian population genetics.

Notwithstanding Yule (1902), Pearson (1904) is sometimes cited as the first paper that gave the Hardy–Weinberg Law for the special case of a gene-frequency of one-half. The twelfth of Pearson's "mathematical contributions to the theory of evolution," it has the ambitious title "On a generalised theory of alternative inheritance, with special reference to Mendel's laws." Pearson assumes that complete dominance is intrinsic to Mendel's theory and puts forward his own theory "based on the conception that the gamete remains pure, and that the gametes of two groups, while they may link up to form a complete zygote, do not thereby absolutely fuse and lose their identity" (Pearson 1904). He then gives "the fundamental formula" connecting parents and offspring as

$$\begin{aligned} a_1a_2 \times a_3a_4 &= (a_1 + a_2)(a_3 + a_4) \\ &= \{a_1a_3,\ a_1a_4,\ a_2a_3,\ a_2a_4\}. \end{aligned}$$

This is none other than Mendel's first law and is Mendel's fundamental discovery, not a novel Pearsonian "general pure gamete theory."

Had Pearson torn himself away from a gene frequency of one-half and also kept to "his" own general theory by not imposing dominance on it, he would have preempted both Weinberg and Hardy, as well as much of Fisher (1918). As it is, the paper is a mathematical development of several of the ideas contained in Yule (1902) and, quite extraordinarily, it nowhere mentions Yule. Instead, it declares "I owe the incentive to this memoir to Professor W. F. R. Weldon, who has already worked at some of the simpler cases and who placed his results entirely at my disposal" (Pearson 1904).

Confining ourselves to the question of Hardy–Weinberg equilibrium, we note that Pearson repeated Yule's result (he does so in the context of multiple loci though, as Provine pointed out, in this case equilibrium is not reached in one generation):

> It is thus clear that the apparent want of stability in a Mendelian population, the continued segregation and ultimate disappearance of the heterozygotes, is solely a result of self-fertilisation; with random cross fertilisation

> there is no disappearance of any class whatever in the offspring of the hybrids, but each class continues to be reproduced in the same proportions (Pearson 1904).

Pearson is here comparing his random-mating result with Mendel's selfing calculation described above. The dominants did not increase in frequency then, nor do they do so now under random mating. After many pages of working out regressions and correlations between relatives on the assumption of complete dominance (for further discussion see Edwards 2008), Pearson ends with a tantalizing footnote:

> Toss two pennies, and the result of $4n$ tossings will closely approximate to the distribution n(HH+2HT+TT). Load one or both coins, and the possible variations will still be HH, HT or TT, but their proportions will be far from n: $2n$: n (Pearson 1904).

He is actually referring to hypothetical departures from his fundamental formula—Mendel's first law—but he had only to think of a departure from a gene frequency of one-half instead and he would have found the Hardy–Weinberg law.

It does seem as though both Yule and Pearson were under the misapprehension that implicit in the Mendelian theory was the assumption that the gene frequency was one-half, for then indeed a 1:2:1 ratio would appear and be maintained. They seem to have been influenced by the fact that Mendel started many of his experiments by breeding from hybrids ($Aa \times Aa$) so that the gene frequencies were indeed one-half for A and a, but of course this has no bearing on what they might be in a population. Provine (1971) states that in 1902 Yule believed that "the 1:2:1 ratio was the *only* stable equilibrium," A and a being equally frequent in the population, but this misleadingly implies that Yule had investigated other gene frequencies and found no stable equilibria.

Pearson (1909) finally arrived at the Hardy–Weinberg law himself, adding the footnote "The stability after the first generation is very obvious, but, as far as I know, was first stated in print by G. H. Hardy [1908]" (Pearson 1909).This is probably the first reference to Hardy's paper.

PUNNETT'S LECTURE AND YULE'S QUESTION

The genesis of Hardy's letter to Science has been described by Punnett (1950), who in 1908 put the genetic problem to him. At that time R. C. Punnett was a Fellow of Gonville and Caius College and a Balfour Student in the Cambridge University Department of Zoology, and since 1903 had been assisting William Bateson with his Mendelian experiments. The circumstances can be described starting from Punnett's account, but with some significant variation where the written record differs from his recollection 41 years later.

On February 28, 1908, Punnett gave a lecture "Mendelism in relation to disease" to the Epidemiological Section of the Royal Society of Medicine in London (Punnett 1908). (In 1950 he mistakenly gave the title as "Mendelian heredity in man.") It was a very full account of Mendelism as it was then understood, principally through the work of Bateson and his colleagues in Cambridge, suitably adjusted to appeal to a medical audience. In the Discussion, which is printed with the paper, M. Greenwood and Yule, associates of Karl Pearson, led the criticism of the "Mendelian school." Yule said that if in man brachydactyly was determined by a dominant gene and random mating assumed, then "in the course of time one would then expect, in the absence of counteracting factors, to get three brachydactylous persons to one normal" but that this was not so.

Here Yule seems to have still been under the misapprehension that implicit in the Mendelian theory was the assumption that the gene frequency was one-half, for then indeed a 3:1 ratio would appear and be maintained.

Be that as it may, in his reply Punnett interpreted Yule as having asked "why the nation was not slowly becoming . . . brachydactylous." (The example of brown and blue eyes was also mentioned, but because Hardy used brachydactyly as the sole example, we do so too.) This was not quite what Yule had suggested, as noted by Crew (1967) in his Royal Society obituary of Punnett, but from both Punnett's (1950) later account and Hardy's letter it is clear that Punnett was perplexed as to why the dominant gene did not continually increase in frequency, and this is the problem he put to Hardy. Yule might easily have corrected him after the meeting, but presumably did not. Punnett (1950) later claimed that he answered that the heterozygotes must also contribute their "quota" of the recessives "and that somehow this must lead to equilibrium," but there is no evidence of this in the printed record of the meeting.

HARDY

G. H. Hardy (Figure 1) was 31 at the time, a Fellow of Trinity College and College Lecturer in Mathematics. He was already destined for a career of great distinction. His classic text *A Course of Pure Mathematics* was first published in 1908 and has been in print ever since. In 1910 he was elected a Fellow of the Royal Society and in 1919 elected to the Savilian Professorship of Geometry at Oxford, returning to Cambridge in 1931 as the Sadlerian Professor of Pure Mathematics. The Savilian Professorship is not in practice restricted to geometry, and Hardy's (1920) inaugural lecture was entitled *Some Famous Problems of the Theory of Numbers.* He remained in Cambridge until he died in 1947, having in 1940 added to his mathematical books *A Mathematician's Apology*, a wistful and enduring account of his personal odyssey, of great literary merit (Hardy 1940).

FIGURE 1.—G. H. Hardy.

Hardy–Weinberg equilibrium is, of course, a mathematical result of embarrassing simplicity, and it would be out of place to dwell here on Hardy's great achievements in pure mathematics, of his long collaboration with J. E. Littlewood and his support of S. Ramanujan, for which see his Royal Society obituary (TITCHMARSH 1949). A valuable personal memoir of Hardy was written by SNOW (1967). What is amusing is the irony of so great a mathematician having delivered and published so simple an answer. For this it is more relevant to understand the social background in Cambridge University before the First World War that led to interactions such as that between Punnett and Hardy.

At the time, and for many years to come, the colleges of the University of Cambridge were for men only, except for Newnham and Girton, which were for women only. Each college maintained fellowships to provide undergraduate teaching and to foster research. Hardy and Punnett were Fellows of Trinity College and Gonville and Caius College respectively, adjacent colleges in the center of town. (Beyond Trinity lies St. John's, where William Bateson was a Fellow.) In the men's colleges most of the Fellows were bachelors "living in," that is, occupying rooms in college, at least in term time. Social life revolved around the common meals, especially the evening "High-Table" dinner with its opportunities for relaxed conversation across the barriers between subjects. It has sometimes been said that Punnett put his genetic question to Hardy at one such dinner, but there is no evidence for this. PUNNETT (1950) simply wrote that on his return to Cambridge from his lecture in London "I at once sought out G. H. Hardy with whom I was then very friendly." He went on to explain that this was not only because they used to play cricket together, but also because they had acted as joint secretaries to a committee that had been lobbying for the retention of Greek in the Cambridge entrance examination. Nothing was more natural than that the wholly unmathematical Punnett should rub shoulders with the leading mathematician of the day.

PUNNETT'S QUESTION AND HARDY'S SOLUTION

Although Hardy opened his short paper with the quotation from Yule given above, adding that "such an expectation would be quite groundless," a later paragraph makes it clear that Punnett's question must have been framed in terms of the puzzle as to why the dominant gene did not continually increase in frequency:

> In a word, there is not the slightest foundation for the idea that a dominant character should show a tendency to spread over a whole population, or that a recessive should tend to die out (HARDY 1908).

Moreover, "I should have expected the very simple point which I wish to make to have been familiar to biologists" (HARDY 1908).

Assuming a large random-mating population, Hardy showed (by "A little mathematics of the multiplication-table type") that if the parental genotypic proportions were p *AA*: $2q$ *Aa*: r *aa*, then they would be $(p + q)^2$: $2(p + q)(q + r)$: $(q + r)^2$ among the offspring. He does not now ask whether the gene frequencies have changed (of course they have not) but, What is the condition that the genotype frequencies have not changed? Presumably he has noted that in general they will have. With four equations (the three genotype frequencies and $p + 2q + r = 1$) and three unknowns, there must be a relation among them. "It is easy to see that . . . this is $q^2 = pr$" (HARDY 1908).

It probably was easy for Hardy the mathematician, but it is as well to prove it, as follows:

Equating the heterozygote frequencies,

$$q = (p + q)(q + r) = q(p + r) + pr + q^2.$$

Rearranging,

$$q^2 = q(1 - p - r) - pr = 2q^2 - pr \quad \text{whence } q^2 = pr.$$

Then he notes that this is true for the offspring generation, and so it and the genotype frequencies will henceforth remain unchanged. He calls this situation "stable" but again the mathematician intervenes. It is only stable in a certain weak sense, in that with a finite population there will always be small deviations from the previous genotypic array, but the new one will be similarly stable. This is not what a mathematician usually means by stable, and Hardy is careful always to qualify this weak sense with inverted commas.

It therefore seems certain that Punnett's question was phrased in terms of the genotype frequencies under random mating, and not the gene frequencies themselves. "I put my problem to him as a mathematical one. He replied that it was quite simple and soon handed to me the now well-known formula $pr = q^2$. Naturally pleased at getting so neat and prompt an answer I promised him that it should be known as 'Hardy's Law'—a promise fulfilled in the next edition of my *Mendelism* (Punnett 1950)." True to his word, the third edition (Punnett 1911) contains a discussion of Hardy's "suggestive contribution." Punnett is quite clear at last:

> The term dominant is in some respects apt to be misleading, for a dominant character cannot in virtue of its dominance establish itself at the expense of a recessive one. Brown eyes in man are dominant to blue, but there is no reason to suppose that as years go on the population of these islands will become increasingly brown eyed. Given equality of conditions both are on an equal footing (Punnett 1911).

Hardy did not use the word "equilibrium" (as Pearson had), nor indeed did Punnett actually use the phrase "Hardy's law" in his book. But Hardy's law it became, and then the Hardy–Weinberg law (Stern 1943).

One of the common embellishments of the story is that Hardy published in the American journal Science because he wanted to hide his involvement in so trivial a mathematical result from his colleagues, but in a letter to Stern in 1950 shown to me by the late C. A. B. Smith, Punnett made it quite clear that the actual reason was "that *Nature* at that time was extremely hostile and refused to publish anything tainted with Mendelism."

Figure 2 shows the offprint of Hardy's letter that belonged to Punnett; the outside being plain, Punnett has written the title in his own hand. His collection of offprints descended to Fisher, his successor as Professor of Genetics, and thence to the departmental library.

BATESON

On October 1, 1908, William Bateson became the holder of the world's first professorship devoted to genetics, at Cambridge University. In his inaugural lecture *The Methods and Scope of Genetics* on October 23 (Bateson 1908) he explained that "[the] Professorship, though bearing the comprehensive title 'of Biology,' is founded with the understanding that the holder shall apply himself to a particular class of physiological problems, the study of which is denoted by the term Genetics" (Bateson 1908) (the word he had himself coined in 1905). Very probably Hardy will have been in the audience, and Punnett certainly. We might have expected some reference to Hardy's law, but alas there is none. The lecture is a completely nonmathematical survey of the new science, memorable for the coining of the phrase "Treasure your exceptions!" sometimes attributed to Darwin:

> Treasure your exceptions! When there are none, the work gets so dull that no one cares to carry it further. Keep them always uncovered and in sight. Exceptions are like the rough brickwork of a growing building which tells that there is more to come and shows where the next construction is to be (Bateson 1908).

The following year Bateson (1909) published his book *Mendel's Principles of Heredity*. Although Hardy is not in the index of authors, his letter to Science is in the bibliography (with the incorrect title "Statistical Results of Mendelian Heredity"). There is no consideration of population questions at all so that Hardy's result is not mentioned, but in Chapter III, "Numerical consequences and recombinations," Bateson (1909) writes "I am obliged to a mathematical friend for the following scheme . . . ," namely the generalization of the 3:1, 9:3:3:1, . . . ratios to any number of dominant loci. It might have been Hardy, but more probably was one of Bateson's colleagues in St. John's College.

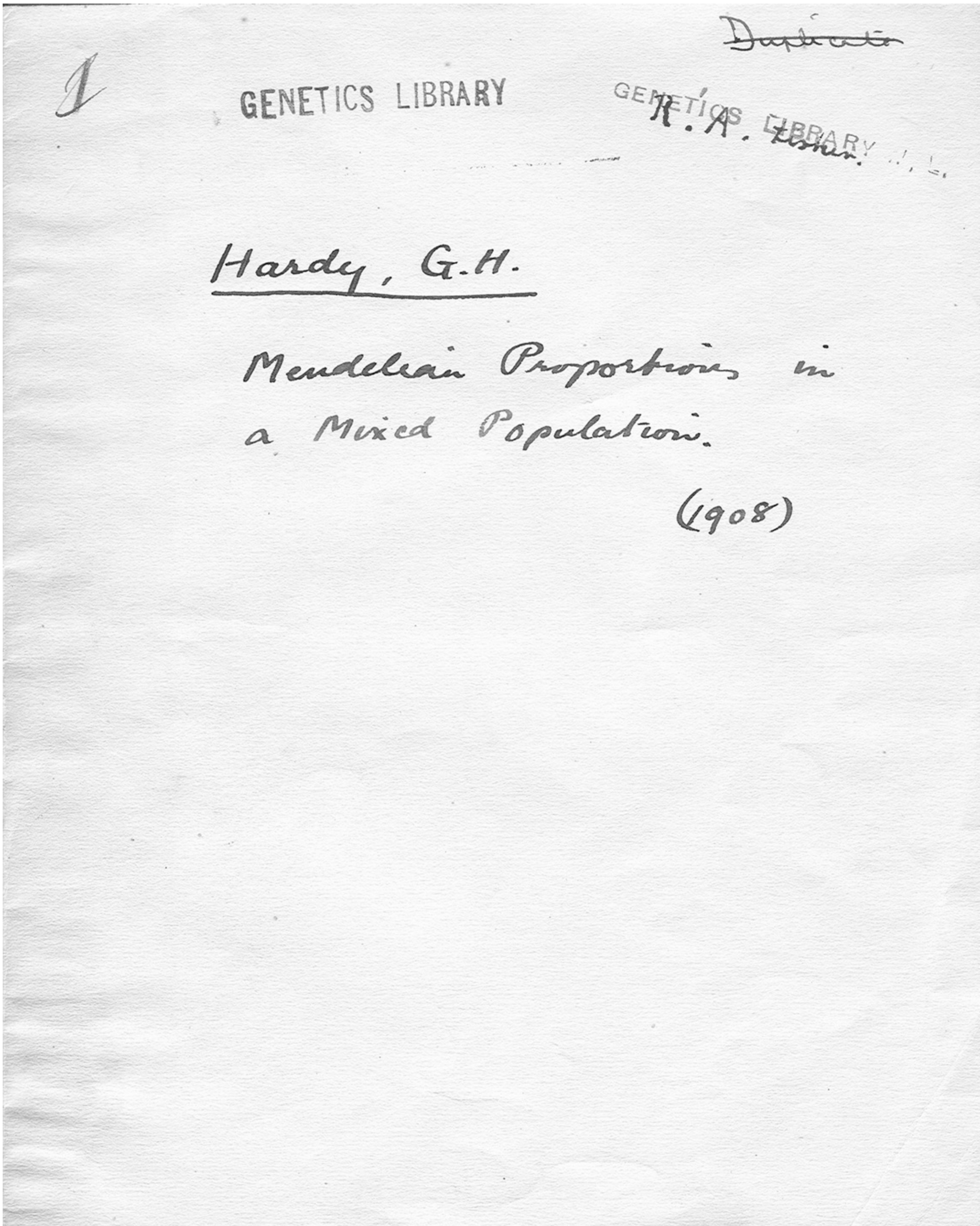
FROM HARDY TO NORTON AND HALDANE

When writing his book *Mimicry in Butterflies*, Punnett (1915) appealed to Hardy for some more mathematical help. He wanted to know the effects of selection at a single Mendelian diallelic locus under random mating, and Hardy, perhaps aware of the amount of computation involved, passed the problem on to his Trinity pupil H. T. J. Norton. The results were published in tabular form in Appendix 1 of Punnett's book (and reprinted in Provine 1971). They were very influential, among other things inspiring J. B. S. Haldane to initiate his long series of papers on selection. Haldane was appointed Reader in Biochemistry at Cambridge in 1923, with a Fellowship of Trinity, and wrote that in 1922 Norton had shown him some calculations that were eventually published in 1928 (Haldane 1927; Norton 1928). Provine (1971) may be consulted for further details, and Charlesworth (1980) for details of "Norton's theorem."

In 1917 Punnett again sought Hardy's help over a similar problem, and this time Hardy himself calculated how slowly a recessive lethal is eliminated from a population, thus apparently discrediting the eugenicists' claim that deleterious recessives could be eliminated in a few generations (Punnett 1917). However, Fisher (1924) countered that these calculations "have led to a widespread misapprehension of the effectiveness of selection."

FISHER

R. A. Fisher never referred to Hardy's law by name, or to Hardy–Weinberg equilibrium, but this was not for



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R. A. ~~Fisher~~

Hardy, G.H.

Mendelian Proportions in a Mixed Population.

(1908)

FIGURE 2.—Punnett's copy of Hardy's letter to Science.

want of admiration of Hardy, "to whom I owe all that I know of pure mathematics" (FISHER 1958). Fisher read the Cambridge Mathematics Tripos in the years 1909–1912, just after the publication of Hardy's *A Course of Pure Mathematics*, and had attended his lectures. The natural points at which to introduce Hardy's name would have been when he derived the equilibrium under selection at a diallelic locus, essentially extending Hardy's mathematics to the case of genotypic selection (FISHER 1922), or later when proving the condition for stability of the equilibrium (FISHER 1930) that he had given in the earlier paper.

An occasion for Fisher mentioning Hardy occurred much later when he was relating an anecdote about him that is worth repeating. Hardy had remarked, at the Trinity High Table, that if a system of axioms allows the deduction of any contradiction, then any proposition whatever can be deduced from it:

> Someone took him up from across the table and said, "Do you mean, Hardy, if I said that two and two make five that you could prove any other proposition you like?" Hardy said, "Yes, I think so." "Well, then, prove that McTaggart is the Pope." "Well," said Hardy, "if two and two make five, then five is equal to four. If you subtract three, you will find that two is equal to one. McTaggart and the Pope are two; therefore, McTaggart and the Pope are one." I gather it came rather quickly (Fisher 1958).

Fisher must have been one of the few people to have had contact with both Hardy and Weinberg. He corresponded with the latter, and on August 29, 1930, wrote in a letter to him "I am sure you will always be honored abroad, and I hope also in your own country for your pioneer work upon the Mendelian or other interpretation of human data."

CONCLUSION

That such a slight problem should have found its way to so great a mathematician as Hardy is an example of the social network within and between the colleges of Cambridge, "the wonderful melting pot of ideas, where astronomers rub shoulders with historians, neurophysiologists with lawyers, and mathematicians with geneticists, statisticians, and others," as Jerzy Neyman wrote in his appreciation of Fisher (Neyman 1967). That it should not have been solved earlier is a reflection of the lack of such a network, indeed of the existence of a great divide, between, on the one hand, Pearson, Yule, Greenwood, and other biometricians in London, and, on the other, Bateson, Punnett, and other Mendelians in Cambridge. These were no mean scientists, and the answer was in Mendel's paper all the time. But happily the delay led to the involvement of Hardy and, because he was presented with the problem as one of the stability of genotype frequencies rather than of gene frequencies, to the law that he shares with Weinberg.

In his peroration to *A Mathematician's Apology* Hardy (1940) wrote "I have never done anything 'useful'. No discovery of mine has made, or is likely to make, directly or indirectly, for good or ill, the least difference to the amenity of the world." We reply that the Hardy–Weinberg law has, on the contrary, been useful to the subject of genetics, a field of great importance to the amenity of the world. Hardy would have been unmoved. Earlier in his masterpiece he had written "The mathematician's patterns, like the painter's or the poet's, must be *beautiful*; the ideas, like the colours or the words, must fit together in a harmonious way" Hardy (1940). The harmony of the equilibrium surely appealed to him.

NOTE ON THE SECONDARY LITERATURE

We have not commented on the very large secondary literature on Hardy–Weinberg equilibrium. Two earlier *Perspectives* articles may, however, be noted: Crow (1988, 1999), the latter being particularly strong on Weinberg. In the former, Crow mistakenly gives Hardy's first name as Geoffrey instead of Godfrey, but this is only a reflection of the fact that Hardy was usually addressed by his surname alone in accordance with custom in Cambridge at that time. When intimates used a Christian name it was in any case the other one, Harold.

A matter from the secondary literature that does merit attention is whether Castle (1903) obtained the Hardy–Weinberg law. Sewall Wright, who was a pupil of Castle's, wrote

> Castle (1903), in the course of a criticism based on a misunderstanding of Yule's [1902] postulates, worked out for the first time the effect of selection in a Mendelian population (selective exclusion of the recessives in each generation). [This is correct.] He also showed (as Sturtevant has recently called to my attention) that if selection ceases, the composition of the randomly bred descendants remains constant thereafter, with genotypic frequencies according to the now familiar binomial-square rule (Wright 1965).

This is unfortunately not correct. By the "binomial-square rule" Wright meant expressions of the form $m^2 AA + 2mnAa + n^2aa$, and Castle did indeed give a number of such *numerical* expressions for the offspring genotypic frequencies resulting from random mating in the course of his selection calculations, with m and n integers. In a footnote he wrote "To simplify the calculation, it is well to remember that the numerical proportions of the various matings possible within a population are expressed by the square of that population" Wright (1965), but he nowhere remarked that the *offspring* conformed to a binomial-square pattern too, and he did not give any formula. When he later stated "In general, *as soon as selection is arrested the race remains stable at the degree of purity then attained*" Wright (1965) (his italics), it was a statement supported by particular examples in which he did not give the genotypic distributions, as Wright suggested, but only the percentage of dominants. It is rather obvious that he knew that the genotypic distribution was also stable, but he did not actually state it. Wright (1965) continued

> Unfortunately, he [Castle] did not stress this [the binomial-square rule] as a basic principle of population genetics, and it did not attract attention. It is now known as the Hardy–Weinberg law because of independent restatements by Hardy and by Weinberg in 1908.

The unavoidable conclusion is that Castle, in what he actually published, did not give any rule or law in anticipation of Hardy and Weinberg. As Pearson (1909) said "The stability after the first generation is very obvious," but it still awaited a clear statement. Castle did certainly perform the first generation-by-generation selection calculations, a remarkable achievement so soon after the rediscovery of Mendel's law and one not repeated until Norton in 1915 as described above.

Sturtevant (1965), in his *A History of Genetics*, made statements about Castle (1903) similar to Wright's, although he mistakenly thought that Yule had made an error that was corrected by Castle.

Finally, in connection with Fisher's (1922) observation that heterozygote advantage leads to balanced polymorphism, mentioned in the section above on Fisher, we note that Provine's (1986) claim that Wright pointed this out the previous year seems to be reading a little too much into a statement by Wright (1921): "Selection of heterozygotes leads to no fixation whatever, however long it may be continued." Wright was simply pointing out that if mating is restricted to heterozygotes, there will always be heterozygotes among the offspring.

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