

Goings on in Mendel's Garden

KENNETH WEISS

The honorable monk probably didn't cheat. But he led us astray in other ways.

Gregor Mendel gave us the tools by which to do modern genetics, and we have a century of progress to show for it. We properly credit Mendel and his peas for showing us the particulate nature of inheritance, but his work both enabled and disabled evolutionary thinking for several decades after its rediscovery. Since the factors he studied didn't change over generations, Mendel's discoveries solved the problem that perplexed Darwin, that blending inheritance would swamp variation and prevent evolution from happening. Yet, for the same reason, Mendel's work impeded evolutionary thought because evolution requires change, and discrete variation was also incompatible with darwinian gradualism. Eventually things were worked out, we got our unified theory (the neodarwinian Synthesis), and it rested on Mendel's discoveries.

Despite his contributions, there has long been a bit of queasiness about Mendel. Almost as soon as his work was discovered in 1900, persistent suggestion arose that the honorable Moravian monk had falsified his data. A recent analysis of these allegations has helped illuminate the issues, and they fall entirely to Mendel's credit.

This vindication is good for Mendel's reputation, and his principles are invoked routinely when inheritance is

discussed. But this may have inadvertently led us astray, in ways for which we are paying a price today. The artificial nature of his experiments lured us into confusing the inheritance of *traits* with the inheritance of *genes*. And this in turn has led to an unwarranted phenogenetic (see Note 1) determinism that impairs our understanding of biology.

BLENDING IN

Mendel wasn't trying to explain evolution. He knew of traits that varied continuously in his experimental pea species, *Pisum sativum*, and appeared to blend in darwinian fashion from one generation to the next. But he wanted to breed agriculturally valuable strains, so he avoided such traits and instead selected strains of pea plants with traits that stably bred true across generations. This enabled him to do his experiments, but it made his analysis conditional, on the chosen characteristics of his particular stocks, an important point we will return to later.

WHAT'S BEEN SAID OF WHAT MENDEL DID

Fairbanks and Rytting (2001) have recently published a fine review of the controversies surrounding Mendel's work and contribution to genetics. Fairbanks and Rytting describe five controversies surrounding Mendel's paper: (1) that Mendel fudged his data to make his results too close to what he expected to be believable as results of the experiments he said he did; (2) that he misleadingly claimed that he



Figure 1. Mendel.

used pea strains that differed only by the single traits he reported for each experiment; (3) that he never actually stated his two famous laws, which were only attributed to him afterward; (4) that Mendel detected, but failed to mention linkage (non-independence of traits), which would have violated his second principle; and (5) whether he was affected by Darwin's *Origin of Species*, a translation of which he is known to have read.

The first is the most important issue, and I'll consider it last. As to the charge that Mendel really didn't have plants that differed only by the single traits as he claimed, Fairbanks and Rytting show that individual strains of peas that are known to have been available to Mendel at the time, in fact bred true, separately, for his traits. Mendel did not study multiple traits in a single experiment and then describe the results as if each trait were

Kenneth Weiss is Evan Pugh Professor of Anthropology and Genetics at Penn State University.

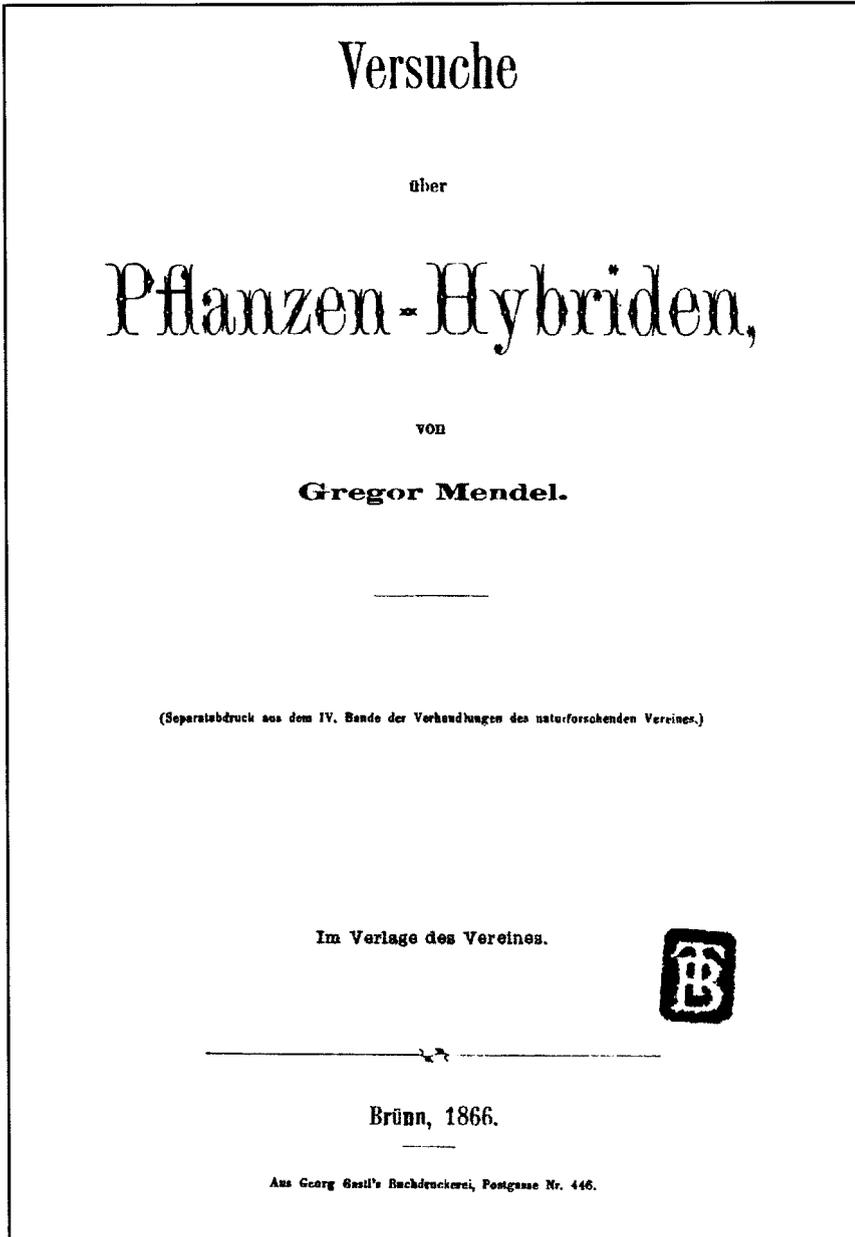


Figure 2. Cover page of Mendel's famous paper. Facsimile courtesy Electronic Scholarly Publishing (www.esp.org).

studied separately. He did what he described.

Mendel's two famous basic principles are: Segregation, that the two copies of a gene in a parent separate and only one is transmitted to any given offspring; and Independent Assortment, that different genes are transmitted independently. Fairbanks and Rytting show that Mendel articulated both principles, and that the allegation that he didn't is based on searches through his paper to find them in modern genetic terms. But

Mendel understood the principles and their importance.

In some experiments, Mendel intentionally studied multiple traits simultaneously. In most of these, the genes for each trait happened to have been on separate chromosomes. But there were instances in which two traits were in fact linked (Table 1). Had he detected that it could have violated his second law. One allegation is that he observed co-inherited traits but failed to report them. However, Fairbanks and Rytting show that the

genes affecting his traits are so far apart on the chromosome that recombination would have been too infrequent for Mendel to have detected their slight correlation with his sample sizes. His choice of traits also appears to have been for uncompromised reasons: they were of botanical importance and differed between strains.

Mendel read *Origin of Species* and made a number of marginal notes in his copy. These notes show that he thought about Darwin's message, but he found little in the book that related to his agronomic objectives, and nothing suggests that his experiments were influenced by Darwin's ideas in any material way.

RESEARCH INTEGRITY OR FALSE ACCUSATION?

As to the cheating scandal, the oft-repeated claim is that Mendel's results fit his expectations too well and must have been cooked. The argument is somewhat intricate, but I can illustrate it with one example (Figure 3). Let A denote the dominant effect, relative to recessive a , so only aa individuals show the recessive trait. Mendel first crossed AA and aa plants, producing all Aa offspring, with the dominant trait. Crossing these offspring with each other generates a next generation with a 2:1 mix of Aa to AA types among dominant plants (plus some recessive aa 's).

However, Mendel had no way to discriminate type among these dominant plants, so he self-fertilized them and sampled 10 offspring from each. If a plant produced 10 dominant offspring, he assigned them to the AA class. This is fine for AA 's. But for an Aa parent, there is a $\frac{1}{4}$ chance that a given offspring will be aa and have the recessive trait, but this means that there is a chance of $1 - (\frac{3}{4})^{10} = 5.6\%$ that an Aa parent produces no recessive offspring among the 10 that Mendel scored. He would thus assign these cryptic Aa 's mistakenly to the AA class. Even if the true expected Aa to AA is 2:1, Mendel's scoring system should have produced a 1.89:1.11 observed ratio. Thus, his results were not just improbably close to 2:1 but that is the wrong answer to be close to. Must he have cheated to get them?

TABLE 1. MENDEL'S GENES

Trait	Gene	Chromosome	Notes
Seed shape	<i>r</i>	7	Smooth dominant to wrinkled
Cotyledon color	<i>i</i>	1	Yellow dominant to green
Seed coat color	<i>a</i>	1	Opaque dominant to colorless
Pod shape	<i>v</i> or <i>p</i>	4 or 6	Inflated dominant to constricted; Which gene Mendel used is not clear
Pod color	<i>gp</i>	5	Green dominant to yellow
Flower position	<i>fa</i>	4	Axillary position dominant to apical
Stem length	<i>le</i>	4	Long dominant to short

Source: Fairbanks and Rytting.

Fairbanks and Rytting analyze these experiments and conclude that Mendel's results were at most only slightly unlikely, and can be explained without cheating, in terms of what is known about pea biology. This largely exonerates Mendel, even from the most serious charge. But I think the whole issue has been greatly overblown in the first place. The reasons to lighten up on the poor monk have to do with his context, with statistical considerations, and with what science is all about.

Mendel was apparently good at analytical thinking and quantification but he worked in a pre-statistics age. The accusation that his goodness-of-fit was too good is based on applications of our notions of formal significance testing, by which criterion his results were too close to occur by chance except rarely. But such tests were not available nor did Mendel have an establishment of rivals and critics preventing him from funding or publishing his work if he didn't satisfy some rather arbitrary rule of significance.

But even if the statistics police are always on patrol in our time, the truth is that these same cops often happily ignore formal tests when they're inconvenient to their favorite hypotheses. For many reasons, some of them legitimate, it is routine, accepted, and even advised by statisticians to discard outliers from analysis, pay heed to "suggestive" *p* values, and demand funding to repeat unsatisfactory results. In his brief paper and presentation at the Natural Science Society of Brunn's 1865 meeting, Mendel openly stated that he was reporting only part—presumably the best part—of his experiments (think what you omit from 20 minute presentations). Besides, it requires some judgment and experience to score Mendel's traits in

peas. And even if he or his assistant selectively pitched (or nibbled) some peas, well, before I put blueberries on my cereal I discard the green ones, but I still say that blueberries are blue.

We should also consider Mendel's historical context. In 1815 William Prout suggested that the weights of pure substances were integral numbers of the weight of hydrogen, of which he hypothesized other substances were composed. Supporters of this view stuck to their guns even in the presence of non-integral relative weights such as that for chlorine, estimated as 35.83. On various rationales, they adjusted their figures toward integral values. Molecular weights are, in fact, integral multiples of their basic components.

Around 1850, Mendel attended lectures in chemistry from a professor Redtenbacker, who had done research on the integral atomic weight of carbon. I think (see Note 2) it quite plausible that Mendel was predisposed to think of integral units of causation for what he observed in plants. Something discrete had to be passed to the gametes of his plants, and indeed Mendel called them "elements". He was after a principle of nature, not a parameter estimate. Everyone knew there was error in experiments (Mendel identified sources of uncertainty in scoring pea traits). New scientific theories typically gain acceptance even in the face of contrary evidence (e.g., Chalmers, 1999; Howson and Urbach, 1993). Mendel was a meticulous, pa-

Generation 1: Cross parental stocks

<u>Parents</u>	<i>AA</i> x <i>aa</i>
<u>Offspring</u>	<i>Aa</i>
<u>Proportion</u>	all <i>Aa</i>

Generation 2: Cross generation 1 offspring

<u>Parents</u>	<i>Aa</i> x <i>Aa</i>
<u>Offspring</u>	<i>AA</i> <i>Aa</i> <i>aa</i>
<u>Proportion</u>	1 2 1

Generation 3: Self-fertilize Generation 2 plants

<u>Parents</u>	<i>AA</i>	<i>Aa</i>	<i>aa</i>
<u>Proportion</u>	1	2	1
<u>Offspring</u>	<i>AA</i>	<i>AA</i> <i>Aa</i>	<i>aa</i>
<u>Proportion</u>	all <i>AA</i>	1 2	1
			all <i>aa</i>

Figure 3. Mendel cheating? Mendel expected a 2:1 ratio of *Aa* to *AA* among the parents with the dominant trait in generation 3 (see text). But by chance, 5.6% of those *Aa* parents will fail to produce any *aa* offspring (boxed in grey), and he would have misclassified them as *AA*, yielding a ratio 1.89:1.11 instead.

tient, detail-minded priest, and it is very unlikely he would truly have fudged data.

And he was right: 2:1 makes theoretical sense; 1.89:1.11 makes none.

WHAT MENDEL DID FOR US

Mendel enabled modern genetics to take off rapidly once his results became known, and we rightly credit him for his perceptive insight. The particulate nature of genetic inheritance is now beyond question and has been confirmed in intimate detail at the molecular level across the spectrum of biological organisms. We also have confirmation of Mendel's specific inferences on peas, and the genes for his traits have been identified (Table 1). The variation for each trait is indeed due entirely to a single gene *in the strains he used*, and the nature of the variation has been shown biochemically to explain the traits themselves and the observed pattern of dominance. For example, the starch-branching enzyme SBEI affects the production of the starch amylopectin; an 800 base-pair insertion in one strain used by Mendel interrupts SBEI, altering the starch's water retention properties, leading to wrinkled peas in *rr* plants. Height is affected by the gene *Le*, for the plant growth factor gibberellin; and homozygous *le* (deficiency) leads to short plants (Figure 4). Green peas are caused by the loss of a metabolic pathway that degrades chlorophyll in mature tissue.

In addition to explaining specific traits, the quick demonstration that Mendel's principles applied to diverse plants and animals helped direct research in basic cell biology, leading to the subsequent discovery of DNA, and to the molecular genetic revolution that is now in full flower. Mendel did a lot for us.

WHAT MENDEL DID TO US

It is important to consider what Mendel might have done to us as well as for us. It's not his fault. He showed that traits could arise in families in a non-blending, law-abiding way. He hypothesized the behavior of the causal factors that might be responsible. It was by no means all luck on



Figure 4. The long and short of Mendel's peas. Lines: Le JI 15, le JI 2682. Source: John Innes Centre data base; www.jic.bbsrc.ac.uk/germplas/pisum/gs4f.htm

Mendel's part that his traits were perfect markers for single genes. He specifically devised experiments in which (we now know) there was one gene with two alleles, each homozygous in one parent, in the strains he studied, with little sensitivity to environmental variation in his monastery garden. He deliberately set up a simplified model of the effects of hybridization. He avoided other traits that behaved less well.

The fact that the traits he selected were perfect markers for genes led to principles that could be used to show the genetic nature of other similarly simplified traits. Archibald Garrod's discovery shortly after 1900 that mendelian rules fit simple "inborn errors of metabolism" in humans started a century-long history of identifying genetic disorders by analysis of family data. Until only about 20 years ago, when direct DNA analysis became practical, we had little way to find genes directly; those we could find were closely tied to simple phenotypes that tracked in families like the traits in Mendel's peas. PKU, cystic fibrosis, and many others are the result.

Mendel's legacy is shown by the fact that to many biologists, "genetic" analysis still means the study of inheritance patterns. We still use his *A/a* notation, and his concepts of dominant and recessive alleles are deeply

rooted in genetic discourse. But this may be a trap as much as a treasure, because success in applying principles Mendel observed in his artificial experiments to human traits tightly controlled by genes has led (I would say lured) us to extend Mendel's very restricted kind of phenogenetic determinism far beyond its original scope.

Like the famous princess, we seem to think we can always detect a mendelian pea no matter how many layers of environmental and other influences may lie over it. This leads to regular public suggestions, if not near promises, that our life's events will be foretold from a DNA chip typed at birth. Even traits with only slight aggregation of risk in families are treated as if they are genetic, and major public as well as private investment is being made in the notion that essentially every human trait can be reduced to tractable mendelian causes. In the future, we'll drop by McMendel's Pharmacy, to receive an individualized cocktail tailored specifically for all that ails us. And we criticize Mendel for stretching the evidence!

It hasn't happened yet, but we'll see whether the genetic determinism into which Mendel innocently seduced us has within it the seed, so to speak, of a new era of eugenics based on molecular rather than folk rationales about the inborn nature of human beings. If so this episode, like those before, will be justified by noble scientific argument, made by leading scientists and anthropologists.

NOT EVEN IN PEAS?

Natural populations vary considerably and most traits are affected by multiple genes, multiple alleles, and multiple environmental effects. Mendel's traits can be produced by other mutations in the same genes or in other genes. For example, the spontaneous mutation rate for the *p* gene is 0.05–0.2%, and mutations at another, *v*, are similar. At least eight known genes affect plant height, and several mutations in the *Le* gene alone have been characterized (with their own particular effects). Mendel's pure dominance effects were also an artifact of his experimental design. He scored his traits dichotomously, but some of the effects are quantitative in

allele-specific ways, or depend on the environment, or are affected by other genes.

Much of this has long been known. Thus, from White (1917): “. . . height of a given variety in any given year is very much influenced by environmental conditions. . . . The environmental conditions which modify height are numerous.” Pea height can vary from about 23 to 360 cm, with variable numbers of short and long internodes (lengths between branches) among plants of similar height. Classifying into height categories is “very unsatisfactory, as it represents a very large number of diverse intermediate types.”

Thus, in natural peadom, Mendel's traits themselves are not caused by single loci, not by single mutations, not by simple recessive inheritance, not just three genotypes, not the same way in all populations, and not the same in all environments. Even Mendel's own traits might not be mappable by sampling from natural populations with a full spectrum of variation, the way we do to study human disease.

DOWN THE GARDEN PATH

Mendel designed his experiments carefully. In human genetics, we too often work with far from comparable conditions. The genotypes underlying complex human traits are not easily inferable from the phenotypes. Human genes have tens or hundreds of alleles that vary among populations, thousands of possible genotypes, and quantitatively varying phenotypic effects.

Relative to human biomedical genetics, what Mendel did is roughly equivalent to characterizing a complex disease from the alleles found in only one family. It's actually worse than that, because unlike peas, human families have not had the variation bred out them for countless generations. This explains the frustrating level of heterogeneity we are discovering in natural human traits. By per-

sisting in the belief that we can mendelize almost anything, we cling Kuhn-ishly to century-old concepts that no longer fit so well.

We do something similar in anthropology when we construct evolutionary genes-for stories for all sorts of traits like intelligence, playing Prisoner's Dilemma, and the diversity of complex morphologies that are our traditional interests. Mendel avoided such traits because they didn't show clear inheritance patterns. But we go further, and extrapolate our genetic stories through eons of natural selection.

The lure of genetic determinism and over-simplification may keep scientists off the streets, but at a cost. It diverts funds from other societal needs, and science from potentially more productive research directions that might develop a better understanding of the nature of complex traits, and how they evolve. That would lead us to view genes not as peas deeply embedded under every princess, but as temporary combinations of alleles in genomes that vary fluidly among people and populations, interacting with transitory environmental factors (including other genomes).

The goings on in Mendel's garden were a lot less suspect than has been suggested. He got things right for good reasons. It is we who may get them wrong, by extending his principles beyond their scope. A misleading, oversimplified, and overdeterministic view of life is one possible consequence. Before being so critical of Mendel, we should examine more critically what's going on in our own backyard.

NOTES

I would welcome any comments on this column: kmw4@psu.edu.

I thank Anne Buchanan and John Fleagle for purging earlier drafts of this column. I thank Daniel Fairbanks for various thoughts and information about Mendel and his work.

1. “Phenogenetic” refers to the causal relationship between genotypes and phenotypes.

2. I found that Sturtevant (1967) made a similar surmise.

CORRECTION

By mistake, the last line in Figure 2 of my column in the first issue of this year (*Evol Anthropol* 11:4–8) was given as (—) when it should have been [—]. If you look at the column, you'll see the difference this makes: in the “anything goes” category, where the entire range from 0 to 1, including the end points, is permissible.

TO READ

Most things discussed here can be profitably explored by web searching.

REFERENCES

- Allen, G. (2001) Essays on science and society. Is a new eugenics afoot? *Science* 294:59–61.
- Chalmers A. (1999) *What Is This Thing Called Science?* Cambridge, Hackett Press.
- Orgel V. (1996) *Gregor Mendel: The First Geneticist*. Oxford, Oxford University Press.
- Fairbanks D and Rytting B. (2001) Mendelian controversies: a botanical and historical review. *Am J Botany* 88:737–752.
- Henig RA. (2000) *The Monk in the Garden*. Boston, Houghton Mifflin.
- Howson C, Urbach P. (1993) *Scientific Reasoning*, 2nd ed. Chicago, Open Court.
- Ingram T, Reid J, Murfet I, Gaskin P, Willis C, MacMillan J. (1984) Internode length in *Pisum*. *Planta* 160:455–463.
- Martin D, Proebsting W, Hedden P. (1997) Mendel's dwarfing gene: cDNAs from the *Le* alleles and function of the expressed proteins. *Proc. Natl. Acad. Sci. USA* 94:8907–8911.
- Sturtevant AH. (1967) Mendel and the gene theory. In Brink RA, ed., *Heritage From Mendel*, pp 11:15. Milwaukee: University of Wisconsin Press.
- Weir B. (1996) *Genetic Data Analysis II*. Sunderland, MA: Sinauer.
- White OE. (1917) Studies of inheritance in *Pisum*. II. The present state of knowledge of heredity and variation in peas. *Proc. Am. Phil. Soc* 56:487–588.
- Weiss K (2000) Consulting the Oracle: reverence but circumspection. *Genetic Epidemiol* 19:468–472.

© 2002 Wiley-Liss, Inc.
Published online in Wiley InterScience
(www.interscience.wiley.com).
DOI 10.1002/evan.10019