Gregor Mendel

Versuche über Pflanzenhybriden

The First Law

The starting material

"In all, 34 more or less distinct varieties of Peas were obtained from several seedsmen and subjected to a two year's trial. All the … varieties yielded perfectly constant and similar offspring; at any rate, no essential difference was observed during two trial years. For fertilization 22 of these were selected and cultivated during the whole period of the experiments. **They remained constant without any exception."**

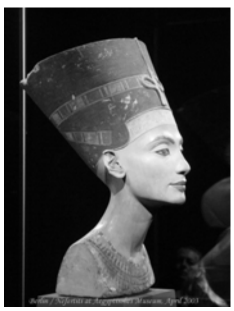
http://www.mendelweb.org/CollText/homepage.html

"Pure-breeding line"

An awkward phrase that is best retired, but never will be.

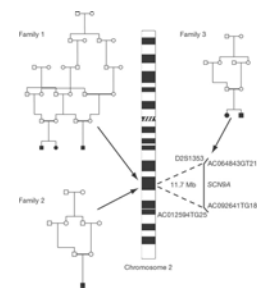
It refers to an organism that exhibits a particular trait (e.g., seed color), and all progeny of that organism (whether it is selfed, or outcrossed to another such organism) also exhibit that trait.

Pure-breeding lines are best made by selfing, or brother-sister crosses (like Nefertiti).



"An *SCN9A* channelopathy causes congenital inability to experience pain" *Nature* Dec. 14, 2006

"The index case for the present study was a ten-year-old child, well known to the medical service after regularly performing 'street theatre'. He placed knives through his arms and walked on burning coals, but experienced no pain. He died before being seen on his fourteenth birthday, after jumping off a house roof."



William Ernest Castle – founder of mouse genetics (UCB 1936-1962)

1. Inbreeding as a tool for making genetically uniform strains of mice that are homozygous for every allele in the genome.

2. Brother-sister matings – makes 12.5% of all loci in the genome homozygous (Clarence Little).

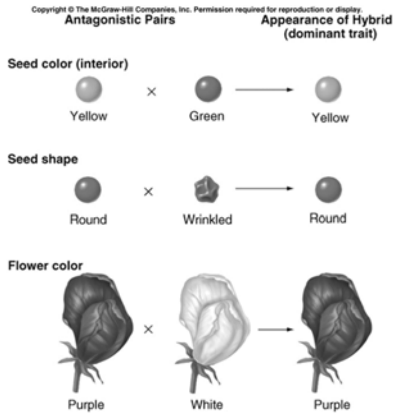
Why? – homework!!

After 40 generations of brother-sister mating, >99.98% of genome is homozygous. By F_{60}, mice are considered genetically identical to one another.

Mendel picked the pea as the system. What **traits** to pick?

"Experiments which in previous years were made with ornamental plants have already provided evidence that the **hybrids, as a rule, are not exactly intermediate between the parental species**. With some of the more striking characters, those, for instance, which relate to the form and size of the leaves, the pubescence of the several parts, etc., the intermediate, indeed, is nearly always to be seen; **in other cases, however, one of the two parental characters is so preponderant that it is difficult, or quite impossible, to detect the other in the hybrid."**

http://www.mendelweb.org/CollText/homepage.html



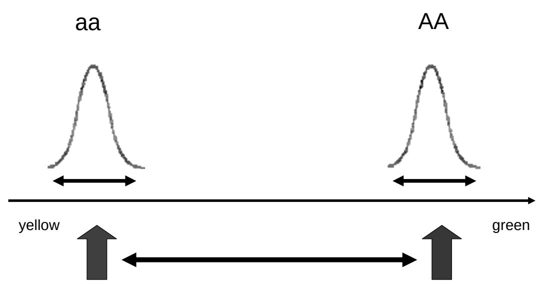
The reaffirmation of a known phenomenon

Mendel is pointing out the distinction between two "types" of traits.

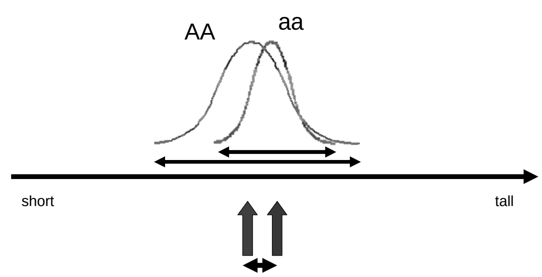
1. The hybrid plant is "intermediate" in phenotype between two parents. For instance, the offspring of a tall and a short plant would be intermediate in height.
2. The hybrid plant has the phenotype like one of the parents. For instance a green x yellow cross yields **only** yellow-seeded plants.

Mendel chose to study "type 2 traits" – a judicious decision. We now know that the laws he discovered in doing so also apply to "type 1" traits, but that fact is considerably more difficult to observe.

Qualitative ("simple") trait



Quantitative ("complex") trait



Not Mendel's fault

In retrospect, we see that the overwhelming majority of traits in humans, other animals, and plants – traits that are of most interest and importance from a public health, and other societally relevant perspectives (height, weight, body plan, facial appearance, skin color) – are quantitative.

Mendel – wisely – chose to study a set of "qualitative" traits because he was a **skilled reductionist**. As a consequence, he discovered two fundamental facts about the functioning of the genetic material. The teaching of genetics, however, **always** begins with Mendel's work, and this creates two erroneous impressions:

1. … that the traits he studied are "controlled by a single gene." That, of course, is not true (all traits are controlled by multiple genes) – he simply worked with plants that were genetically different from each at only one locus out of the many required for the development of the trait. We shall return to that point shortly.
2. … that simple Mendelian relationships of recessivity and dominance between alleles, and "one gene-one trait" correlations he – supposedly – observed are ubiquitous in Nature. "She has her mother's eyes." "He gets his brains from his Dad." Neither trait – eye color nor "intelligence" – exhibit simple Mendelian inheritance, yet most people assume otherwise.

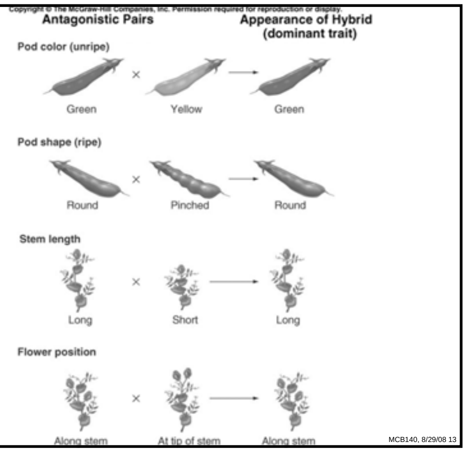
The genesis of the famous term

"… **in other cases, however, one of the two parental characters is so preponderant that it is difficult, or quite impossible, to detect the other in the hybrid.**

This is precisely the case with the Pea hybrids. In the case of each of the 7 crosses the hybrid-character resembles that of one of the parental forms so closely that the other either escapes observation completely or cannot be detected with certainty. This circumstance is of great importance in the determination and classification of the forms under which the offspring of the hybrids appear. Henceforth in this paper those characters which are transmitted entire, or almost unchanged in the hybridization, and therefore in themselves constitute the characters of the hybrid, are termed the *dominant*, and those which become latent in the process *recessive*. The expression "recessive" has been chosen because the characters thereby designated recede or entirely disappear in the hybrids, but nevertheless reappear unchanged in their progeny, as will be demonstrated later on."

"In der weiteren Besprechung werden jene Merkmale, welche ganz oder fast unverändert in die Hybride-Verbindung übergehen, somit selbst die Hybriden-Merkmale repräsentiren, als dominirende, und jene, welche in der Verbindung latent werden, als recessive bezeichnet. Der Ausdruck "recessiv" wurde desshalb gewählt, weil die damit benannten Merkmale an den Hybriden zurücktreten oder ganz verschwinden, jedoch unter den Nachkommen derselben, wie später gezeigt wird, wieder unverändert zum Vorscheine kommen."

http://www.mendelweb.org/CollText/homepage.html

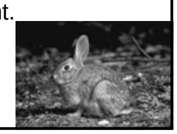


Inverting the direction of the cross does not alter the phenotype of the hybrid

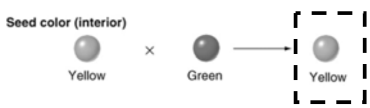
"All experiments proved further that it is entirely immaterial whether the dominating trait belongs to the seed plant or to the pollen plant; the form of the hybrid remains identical in both cases."

Recall Leeuwenhoek's "proof" using grey rabbits that sperm provides all the genetic material, and the egg solely provides nourishment.

Eeeh, what's up with THAT, doc?



What to do with the hybrid (i.e., the F1 plants)?



Mendel decided to let them self (which *Pisum sativum* does naturally, thank you very much). He then grew the progeny (the F2) and did precisely what he promised: he counted the number of phenotypic classes in this F2, and measured the ratio.

The data

Expt. 1. Form of seed. -- From 253 hybrids 7324 seeds were obtained in the second trial year. Among them were 5474 round or roundish ones and 1850 angular wrinkled ones. Therefrom the ratio 2.96:1 is deduced.

Expt. 2. Color of albumen. -- 258 plants yielded 8023 seeds, 6022 yellow, and 2001 green; their ratio, therefore, is as 3.01:1.

Expt. 3. Color of the seed-coats. -- Among 929 plants, 705 bore violet-red flowers and gray-brown seed-coats; 224 had white flowers and white seed-coats, giving the proportion 3.15:1.

Expt. 4. Form of pods. -- Of 1181 plants, 882 had them simply inflated, and in 299 they were constricted. Resulting ratio, 2.95:1.

Expt. 5. Color of the unripe pods. -- The number of trial plants was 580, of which 428 had green pods and 152 yellow ones. Consequently these stand in the ratio of 2.82:1.

Expt. 6. Position of flowers. -- Among 858 cases 651 had inflorescences axial and 207 terminal. Ratio, 3.14:1.

Expt. 7. Length of stem. -- Out of 1064 plants, in 787 cases the stem was long, and in 277 short. Hence a mutual ratio of 2.84:1. In this experiment the dwarfed plants were carefully lifted and transferred to a special bed. This precaution was necessary, as otherwise they would have perished through being overgrown by their tall relatives. Even in their quite young state they can be easily picked out by their compact growth and thick dark-green foliage.

A bit of metaanalysis

"In this generation there reappear, *together with the dominant* characters, also the recessive ones with their peculiarities fully developed, and this occurs in the definitely expressed average proportion of 3:1, so that among each 4 plants of this generation 3 display the dominant character and one the recessive.

This relates without exception to all the characters which were investigated in the experiments.

The angular wrinkled form of the seed, the green color of the albumen, the while color of the seed-coats and the flowers, the constrictions of the pods, the yellow color of the unripe pod, of the stalk, of the calyx, and of the leaf venation, the umbel-like form of the inflorescence, and the dwarfed stem, **all reappear in the numerical proportion given, without any essential alteration**.

Transitional forms were not observed in any experiment."

Brilliant in Brünn

"The dominant character can have here *double meaning*; namely, that of a parental character, or a hybrid-character. In which of the two meanings it appears in each separate case can only be determined by the following generation. As a parental character it must pass over unchanged to the whole of the offspring; as a hybrid-character, on the other hand, it must maintain the same behavior as in the first generation."

Mendel's papers were burned shortly after his death, and we don't have access to his lab notebooks.

We shall therefore never know, whether this was brilliant foresight, or whether he generated the F3, and then let the data tell him, what's going on.

He says here that an F2 plant that looks like one of the parents can, in fact, be homozygous for the dominant allele, OR heterozygous.

He went ahead to prove that, by generating that F3.

Analysis of the grandchildren

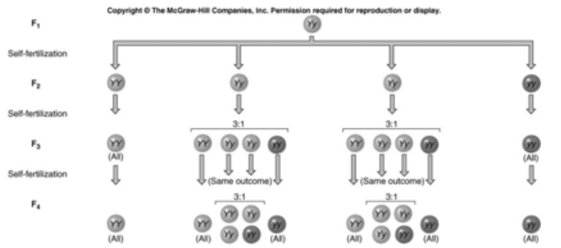


Fig. 2.12

"Those forms which in the first generation exhibit the recessive character do not further vary in the second generation as regards this character; they remain constant in their offspring.

It is otherwise with those which possess the dominant character in the first generation. Of these *two*-thirds yield offspring which display the dominant and recessive characters in the proportion of 3:1, and thereby show exactly the same ratio as the hybrid forms, while only *one*-third remains with the dominant character constant."

Mendel, humble son of a peasant family, pollinating textbooks all over the world for the rest of time with his nomenclature

"The ratio of 3:1, in accordance with which the distribution of the dominant and recessive characters results in the first generation, resolves itself therefore *in all experiments into the ratio of 2:1:1*. …

If **A** be taken as denoting one of the two constant characters, for instance the dominant, **a** the recessive, and **Aa** the hybrid form in which both are conjoined, the expression

A + 2Aa + a

shows the terms in the series for the progeny of the hybrids of two differentiating characters."

And now (drum roll) – the first law

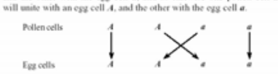
"Experimentally, therefore, the theory is confirmed that *the pea hybrids form egg and pollen cells which, in their constitution, represent in equal numbers all constant forms which result from the combination of the characters united in fertilization*. "

"Es ist daher auch auf experimentellem Wege die Annahme gerechtfertigt, *dass die Erbsen-Hybriden Keim- und Pollenzellen bilden, welche ihrer Beschaffenheit nach in gleicher Anzahl allen constanten Formen entsprechen, welche aus der Combinirung der durch Befruchtung vereinigten Merkmale hervorgehen*."

The simplest case is afforded by the developmental series of *each pair of differentiating characters*. This series is represented by the expression *A*+2*Aa*+*a*, in which *A* and *a* signify the forms with constant differentiating characters, and *Aa* the hybrid form of both. It includes in three different classes four individuals. In the formation of these, pollen and egg cells of the form *A* and *a* take part on the average equally in the fertilization; hence each form [occurs] twice, since four individuals are formed. There participate consequently in the fertilization

The pollen cells: *A* + *A* + *a* + *a*,
The egg cells: *A* + *A* + *a* + *a*.

It remains, therefore, purely a matter of chance which of the two sorts of pollen will become united with each separate egg cell. According, however, to the law of probability, it will always happen, on the average of many cases, that each pollen form *A* and *a* will unite equally often with each egg cell form *A* and *a*, consequently one of the two pollen cells *A* in the fertilization will meet with the egg cell *A* and the other with the egg cell *a*, and so likewise one pollen cell *a* will unite with an egg cell *A*, and the other with the egg cell *a*.



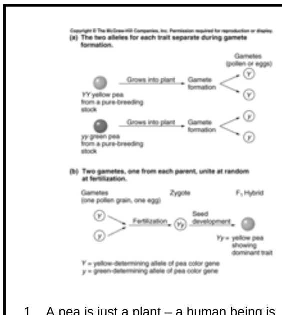
The result of the fertilization may be made clear by putting the signs for the conjoined egg and pollen cells in the form of fractions, those for the pollen cells above and those for the egg cells below the line. We then have

$$\frac{A}{A} + \frac{A}{a} + \frac{a}{A} + \frac{a}{a}.$$

In the first and fourth term the egg and pollen cells are of like kind, consequently the product of their union must be constant, namely *A* and *a*; in the second and third, on the other hand, there again results a union of the two differentiating characters of the stocks, consequently the forms resulting from these fertilizations are identical with those of the hybrid from which they sprang. *There occurs accordingly a repeated hybridization*. This explains the striking fact that the hybrids are able to produce, besides the two parental forms, offspring which are like themselves *A*/*a* and *a*/*A* both give the same union *Aa*, since, as already remarked above, it makes no difference in the result of fertilization to which of the two characters the pollen or egg cells belong. We may write then

$$\frac{A}{A} + \frac{A}{a} + \frac{a}{A} + \frac{a}{a} = A + 2Aa + a.$$

This represents the average result of the self-fertilization of the hybrids when two differentiating characters are united in them. In individual flowers and in individual plants, however, the ratios in which the forms of the series are produced may suffer not



1. A pea is just a plant – a human being is, well, a human being – like you and I, with feelings, rights, dreams …
2. That said, the first important lesson to be acquired from this is the importance of model systems – recall Mendel's "unity of organic life in important things is beyond doubt."
3. The second important lesson is the fact that – in very specific cases, and with carefully constructed qualifiers – clinically relevant conditions in humans are transmitted in mendelian fashion, and follow Mendel's first law.

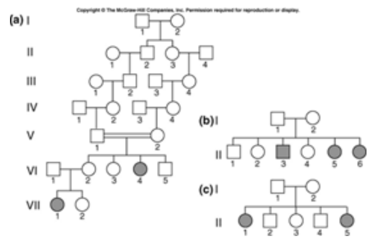
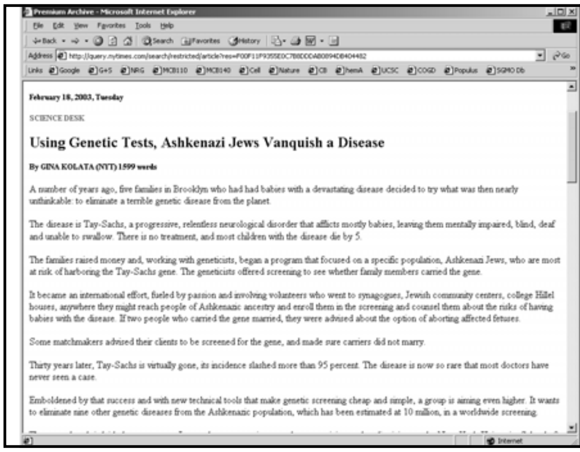


Fig. 2.22



Premium Archive - Microsoft Internet Explorer

February 18, 2003, Tuesday

SCIENCE DESK

Using Genetic Tests, Ashkenazi Jews Vanquish a Disease

By GINA KOLATA (NYT) 1599 words

A number of years ago, five families in Brooklyn who had had babies with a devastating disease decided to try what was then nearly unthinkable: to eliminate a terrible genetic disease from the planet.

The disease is Tay-Sachs, a progressive, relentless neurological disorder that afflicts mostly babies, leaving them mentally impaired, blind, deaf and unable to swallow. There is no treatment, and most children with the disease die by 5.

The families raised money and, working with geneticists, began a program that focused on a specific population, Ashkenazi Jews, who are most at risk of harboring the Tay-Sachs gene. The geneticists offered screening to see whether family members carried the gene.

It became an international effort, fueled by passion and involving volunteers who went to synagogues, Jewish community centers, college Hillel houses, anywhere they might reach people of Ashkenazic ancestry and enroll them in the screening and counsel them about the risks of having babies with the disease. If two people who carried the gene married, they were advised about the option of aborting affected fetuses.

Some matchmakers advised their clients to be screened for the gene, and made sure carriers did not marry.

Thirty years later, Tay-Sachs is virtually gone, its incidence slashed more than 95 percent. The disease is now so rare that most doctors have never seen a case.

Emboldened by that success and with new technical tools that make genetic screening cheap and simple, a group is aiming even higher. It wants to eliminate nine other genetic diseases from the Ashkenazic population, which has been estimated at 10 million, in a worldwide screening.

Brilliant in Brünn, part II

"With Pisum it was shown by experiment that the hybrids form egg and pollen cells of *different* kinds, and that herein lies the reason of the variability of their offspring.

If it chance that an egg cell unites with a *dissimilar* pollen cell, we must then assume that between those elements of both cells, which determine opposite characters some sort of compromise is effected. The resulting compound cell becomes the foundation of the hybrid organism the development of which necessarily follows a different scheme from that obtaining in each of the two original species.

With regard to those hybrids whose progeny is *variable* we may perhaps assume that between the differentiating elements of the egg and pollen cells there also occurs a compromise, in so far that the formation of a cell as the foundation of the hybrid becomes possible; **but, nevertheless, the arrangement between the conflicting elements is only temporary and does not endure throughout the life of the hybrid plant**. Since in the habit of the plant no changes are perceptible during the whole period of vegetation, we must further assume that it is only possible for the differentiating elements to liberate themselves from the enforced union when the fertilizing cells are developed. In the formation of these cells all existing elements participate in an entirely free and equal arrangement, by which it is only the differentiating ones which mutually separate themselves. In this way the production would be rendered possible of as many sorts of egg and pollen cells as there are combinations possible of the formative elements."

This is stunning in a way that the history of biology has not seen before. What Mendel says is the following:

An organism that happens to be heterozygous for a locus carries two distinct alleles of that gene. The two alleles do not change each other's nature – for the time while they are stuck in the same nucleus. Then, when their carrier – the organism – makes gametes, the two alleles become separated again.

"Brilliant" isn't strong enough
This is "swish central"
Nothing but net.

Mendel's data showed – to him – that in a heterozygote, the two alleles – A and a – remain DISTINCT and SEPARATE.

They reach a compromise for the life of the plant, but then, during gametogenesis, they go their separate ways, unchanged.

To describe this incredibly simple idea as influential would be akin to calling Michael Jordan a "pretty good shooting guard."

Sadly, this idea sat on the bench for the entire 1865-1900 season. More on why that happened – shortly.

A useful term

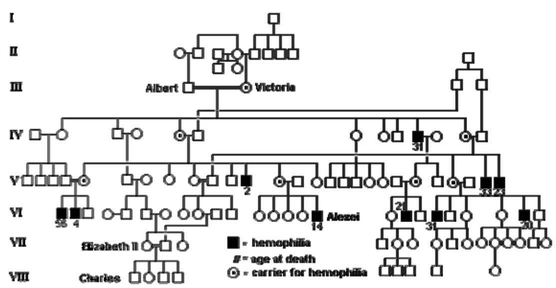
If a **trait** follows in its inheritance Mendel's first law (i.e., Mendelian ratios of phenotypes are observed in pedigrees), that phenomenon is described as "simple Mendelian inheritance" (SMI).

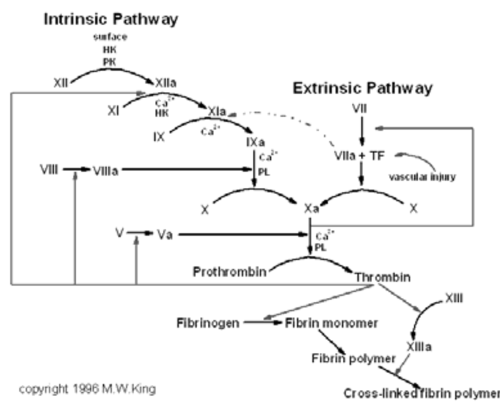
Examples: cystic fibrosis; sickle cell anemia; hemophilia A.

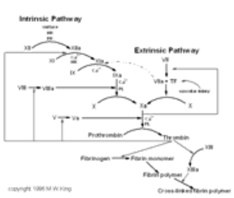
An awful, awful term: "monogenic trait"

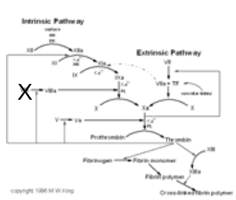
If a trait follows SMI – what does that say about its genetic architecture?

A **highly** pernicious school of lack of thought in biological instruction uses the term "monogenic trait." It is most unfortunate.









In what sense is blood clotting a "monogenic" trait?

In no sense at all.

What is "simple" is the genetic DIFFERENCE between an unaffected individual and an individual who has hemophilia. It can be as small as a single base pair change.

In other words, what the phenotype tracking allows us to do is look at **the genetics of the difference between the genotypes of the organisms with respect to the trait under study**.

If a particular phenotype follows SMI, then all that says is:

With respect to the trait under study, the difference in genotype between an organism **with** that phenotype and **without** it is due to a genetic difference at a single position in the genome (="a single locus").

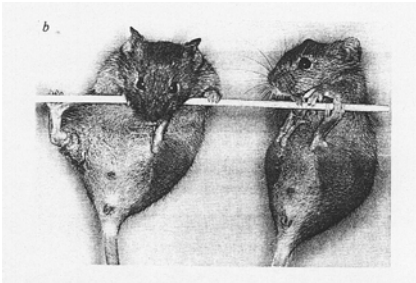
Nothing can be learned from this analysis about the number of genes that are required for that phenotype to develop, or about the role this particular gene plays in having this phenotype develop.

PKU, for example, has to do with the breakdown of aromatic amino acids, and its lack causes mental retardation. What is the **specific** role of phenylalanine breakdown in cognition?

Manhood – a monogenic trait

Note: SRY directly causes the conversion of a female embryo to a male one

XY XX+Sry transgene



Koopman et al. (1991) *Nature* **351:** 117.

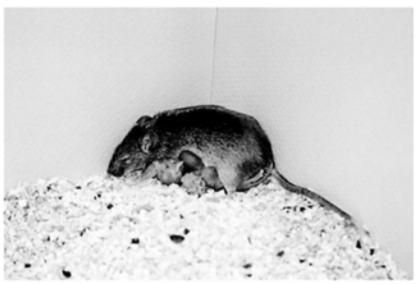
Motherhood – a monogenic trait?!

A Defect in Nurturing in Mice Lacking the Immediate Early Gene *fosB*

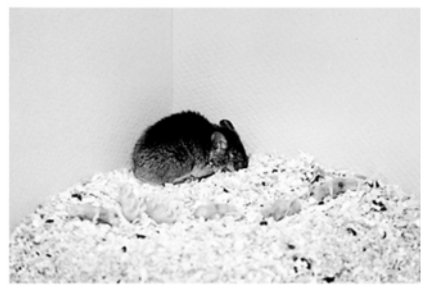
Brown et al.

Cell, Vol. 86, 297–309, July, 1996

C



D



In other words

"Mendelian inheritance" **of traits (note: OF TRAITS)** is largely the exception, not the rule in Nature.

Mendel made two titanic contributions to science:

1. From an **epistemological** perspective, he created a fundamentally novel, enormously powerful experimental paradigm, one that replaces all previous heuristic, trial-and-error-based efforts in this field with a methodical, hypothesis-driven, rigorous quantitation-based approach, in which one sets up controlled crosses, determines the number of phenotypic classes that results from those crosses, analyses their incidence in each generation separately, and determines the ratios of organisms that fall into each class. This – to the letter – remains the core of the genetic research paradigm to this day. It is astonishingly powerful, as you shall see.
2. From an **ontological** perspective, he discovered two of the three most important principles of the behavior of genes (the equal segregation into gametes of two alleles of a gene during gametogenesis; and the independence of the behavior of two distinct genes in this process). The third – linkage – was discovered in 1906 by Bateson and Punnett, and we will discuss it at great length shortly. **All autosomal genes obey Mendel's first law, and all unlinked genes obey Mendel's second law.**

One more thing

Mendel was the first to realize that heredity can be studied quite successfully without any understanding of the **molecular** mechanisms that underlie genetic processes.

As you will see in Prof. Garriga's section and in Prof. Brem's section, this allows geneticists to study and understand highly complex phenomena (e.g., embryonic development; gene regulation; the control of cell division) without significant (or, frequently, any) regard to the physicochemical processes that underlie those phenomena.

More on that in parts II and III of this class.

"What are the genes? What is the nature of the elements of heredity that Mendel postulated as purely theoretical units? … Frankly, these are questions with which the **working geneticist** has not much concern himself…*

If the gene is a material unit, it is a piece of a chromosome; if it is a fictitious unit, it must be referred to a definite location in a chromosome. … Therefore, it makes no difference in the actual work in genetics which point of view is taken."

T.H. Morgan

The Relation of Genetics

to Physiology and Medicine

Nobel Lecture, June 4, **1934**

* Pause for a second and reread this – Thomas Hunt Morgan, the greatest American geneticist of all time, probably the second greatest geneticist, period, here is saying that IT DOES NOT MATTER, what "the genes" are made of, to someone who studies them!! This is both astonishing and true.

Next time

1. Mendel's 2nd law
2. The danger of respecting authority
3. Enter the chromosome