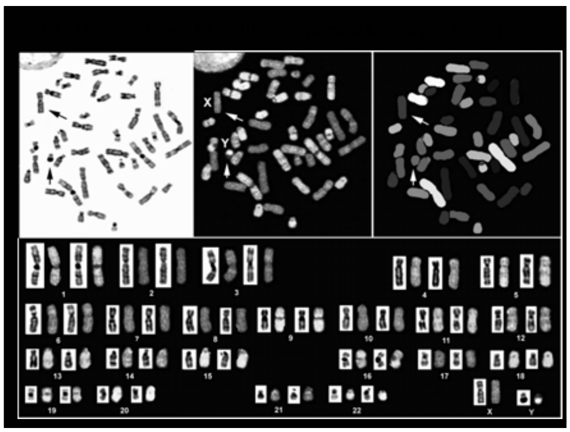
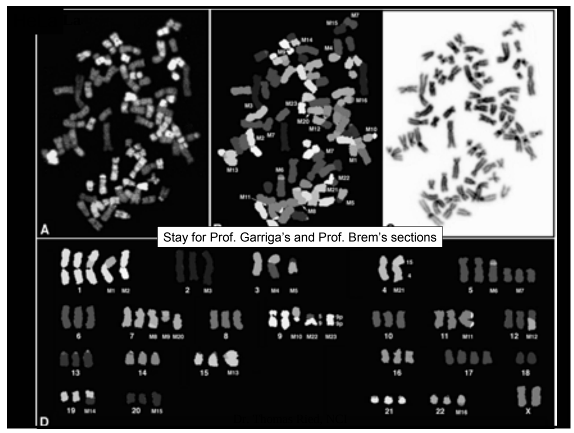
MCB 140 – Genetics





Stay for Prof. Garriga's and Prof. Brem's sections

“Cancer Free at 33, but Weighing a Mastectomy”

Deborah Lindner, 33, did intensive research as she considered having a preventive mastectomy after a DNA test.

The New York Times, Sunday, Sep. 16, 2007

60-80%

The New York Times, Sunday, Sep. 16, 2007

Generations of the Price family have been affected by a mutation in the BRCA1 gene that significantly raises the risk of breast and ovarian cancer. A parent who carries the defective gene has a 50 percent chance of passing it on to his or her children. In 2002, Christie Veale became the first family member to get a DNA test that revealed she had inherited the mutation from her mother. As many of her relatives followed, they have made different choices about how to manage their genetic predisposition to the life-threatening condition.

The New York Times, Sunday, Sep. 16, 2007

Gregor Mendel (1822-1884), and his garden in Brno (Czech Republic)

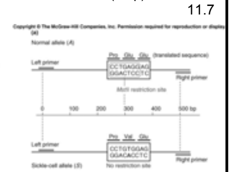
Nov. 17, 2007

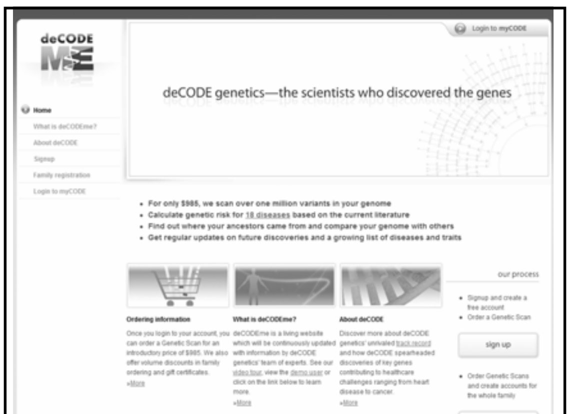
Single nucleotide polymorphism (SNP – pronounced “snip”): 1:1,000

11.25

A SNP that is also a RFLP (rifflip)

11.7





Decode’s claim

“Through a variety of sources, including deCODE genetics own pioneering research in population genetics, we have collected and annotated the most accurate and validated information available on genetic variations which have been associated with an average, higher or lower risk of common diseases. **We will give you both detailed scientific background and the means to study how this knowledge applies to you.**

Our current list of diseases includes: Age-related Macular Degeneration, Asthma, Alzheimer's Disease, Atrial Fibrillation, Breast Cancer, Celiac Disease, Colorectal Cancer, Exfoliation Glaucoma XFG, Crohn's Disease, Multiple Sclerosis, Myocardial Infarction, Obesity, Prostate Cancer, Psoriasis, Restless Legs, Rheumatoid Arthritis, Type 1 Diabetes and Type 2 Diabetes. The disease list will be updated continuously as new discoveries are made.”

Emphasis mine – fdu. My evaluation of said claim:

Disingenuous (a definition from Merriam-Webster):

- lacking in candor;
- also : giving a false appearance of simple frankness : calculating

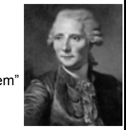
A few terms from the “detailed scientific background”

- Haplotype
- Linkage disequilibrium
- Penetrance
- Expressivity
- Epistasis
- Norm of reaction
- Narrow-sense heritability
- Odds ratio

Two problems

Pierre de Beaumarchais:
The Barber of Seville (1775), The Marriage of Figaro (1784)

“It is not necessary to understand things in order to argue about them”



“Most ignorance is willful” (Bill Watterson)

Ontology vs. epistemology

“The way things are vs. the way we go about understanding, how things are.”

MCB 140 aims to educate MCB majors in not just key *facts* about the functioning of the genetic material in processes of heredity, ontogeny, and disease – but also in the power and the *limitations* of the methods that are used to obtain those facts.

MCB140 – an outline

Part 1: the “classics” – Mendel, Morgan, Beadle-Tatum – the black box of heredity becomes semi-transparent

Part 2 (prof. Gian Garriga): the art and craft of genetics – mutations and genetic screens – from a trait to mechanism – putting together a **pathway**

Part 3 (prof. Rachel Brem): quantitative genetics (“complex traits”).

What to do so as to do well

1. Attend class.
    1. Note: reliance on the fact that many lectures are on the web, hence can be “crammed” at the last minute is a 100%-guaranteed recipe for failure.
    2. Further note: some of the exams will be open-book. This means that information is less important that understanding. Again, postponement of studying to the last minute is a recipe for failure. You have been warned.
2. Keep up with the reading.
3. Do all problem sets.
4. Attend discussion section.
5. Study hard and do well on all the quizzes.
6. Ask the GSIs questions
7. E-mail the faculty: urnov ЭТ berkeley ДОТ edu

Observable phenomena, explainable and not

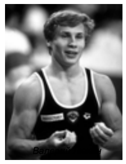
1. Gravity – not understood at all.
2. The color of the sky – understood, but highly technical. ~λ^{-4} (elastic Rayleigh scattering):
   http://hyperphysics.phy-astr.gsu.edu/Hbase/atmos/blusky.html
3. Heredity – understood, and quite simple

→ For millenia, the curse of Yogi Berra – *can* you observe a lot by “just watching”? – prevented the solution from being found

Children “look like their parents”:

Diana Ross – the Supremes

… and “act like their parents”:



Nastia Liukin

→ “It’s All in the Genes” *New York Times*, 5/2/04

Heredity: “**blending** inheritance”?

“The problem was not that thinkers did not look for similarities between the generations, **but that they did**, and were understandably confused by what they saw. Human families provided striking, highly contradictory and apparently inconsistent evidence — children sometimes looked like one parent, **sometimes a mixture of the two**, sometimes like neither and sometimes like their grandparents.”

Cobb *NRG 7:* 953.

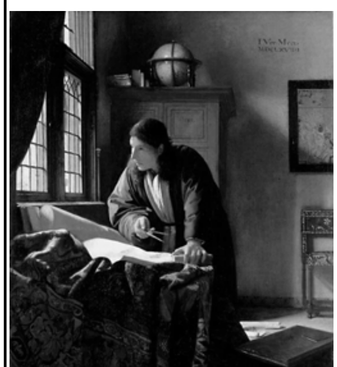
Surprisingly to the modern eye, no one in the seventeenth century argued that eggs and sperm represented complementary elements that made equivalent contributions to the offspring. Instead, the next 150 years were dominated by either 'ovist' or 'spermist' visions of what eventually became known as 'reproduction' (the term was coined only in 1745) (Ref. 7). Each view considered that only one of the two parental components provided the stuff of which new life was made, with the other component being either food (as the spermists saw the egg), or a force that merely 'awoke' the egg (as the ovists saw the spermatozoa).

There were many reasons underlying this apparent scientific dead end. For example, in chickens, the two elements did not seem to be equivalent at all: there was a single enormous egg, which was apparently passive, whereas the 'spermatic animals' were microscopic, incredibly active, and present in mind-boggling numbers. Ultimately, however, the reason that late seventeenth-century thinkers did not realize what to us seems blindingly obvious — that both eggs and sperm make equal contributions to the future offspring — **was that there was no compelling evidence to make them appreciate this.**

Victor Hartmann
-- the drawing that inspired Mussorgsky to write the “Ballet of the Unhatched Chicks” from *Pictures at an Exhibition*

→ The power of the scientific method

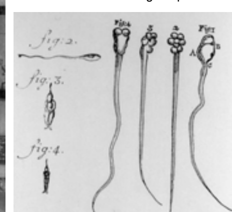
Cobb *NRG 7:* 953.



Jan Vermeer – *The Astronomer* (1688)

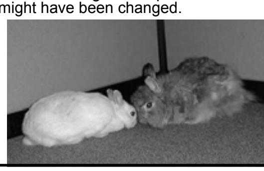
1677

Leeuwenhoek’s drawing of sperm:



In a rare experimental study of resemblance, Leeuwenhoek provided yet another example of the way characters appeared in each generation, and added to the prevailing perplexity. Using what could have been a tractable model — rabbits — Leeuwenhoek was surprised to find that a grey male wild rabbit could give rise to only grey offspring. But Leeuwenhoek argued that spermatozoa were the sole source of the future animal, so his strange finding from rabbits became "...a proof enabling me to maintain that the foetus proceeds only from the male semen and that the female only serves to feed and develop it."9 In other words, there was no relation between both parents and the offspring, but simply between father and offspring, which was represented by the little animal in the male semen. The father was grey, so the offspring were inevitably grey, thought Leeuwenhoek.

It is tempting to imagine that if he had done the reciprocal cross, using a grey female wild rabbit, or if he had studied the grandchildren of his grey male, Leeuwenhoek might have paused for thought and the course of science might have been changed.

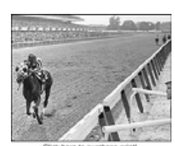


Cobb *NRG 7:* 953.

At the heart of agricultural practice is the assumption that, as Thomas Blundeville, an author with an interest in horse breeding, mathematics and navigation, put it in 1566: "...it is naturally geven to every beast for the moste parte to engender hys lyke."17 However, as Blundeville indicated, this was not always the case, and until the seventeenth-century studies on generation, it was not even clear that it applied to all organisms. More surprisingly, until the second half of the eighteenth century, there does not seem to have been any explicit attempt to exploit this phenomenon; selective breeding, in terms of a conscious decision to manipulate the stock of a domesticated organism, was not widespread, nor was it transformed into a theory. Breeders' 'knowledge' that like bred like was partial and entirely **heuristic**: they were concerned with what worked, not why18.

From the seventeenth-century, breeders tended to use the term 'blood' to describe the quality that apparently lay behind the characters of an animal. But, as with a royal 'bloodline', this was a vague, semi-mystical view of the power of an imprecise quality, rather than a recognition of the hereditary transmission of characters. This confusion was translated into practice: eighteenth-century racehorse breeders would not cross two successful racehorses, creating a 'thoroughbred' stock, but would instead cross racing stallions with local mares18.

Secretariat – to fans of horse racing, the analog of Ted Willams and Michael Jordan



Cobb *NRG 7:* 953.

Word of the day: heuristic

"A method based on empirical information that has **no explicit rationalization**"

"A computational method that uses **trial and error methods** to approximate a solution for computationally difficult problems"

"Grrrrr"

Buffon was interested in the problem of hybrids, but chose to work with quadrupeds. It turned out to be difficult to do a controlled cross. For instance, during an attempt to mate a wolf with a dog, the female wolf ate the dog she was supposed to mate to, and then mauled the coachman.

Georges-Louis LECLERC, comte de BUFFON (1707-1788)
One of the great naturalists of all time

R. Olby *Origins of Mendelism*

Canis lupus

Joseph Kölreuter (1761): plants as a **model system**

- Plant hybridization: 500 different hybridizations involving 138 species.
- **"The experimental study of genetics may be said to date from the work which Koelreuter described it."**
- Studied both F1 and F2 plants in crosses.
- "When Kolreuter compared them, he found a striking contrast. F1 hybrids for any given cross were alike, and in most of their characters were intermediate between the two parental species. F2 and back-crossed hybrids were all different, and they tended to be less like their parental hybrids and more like one or other of the originating species."

R. Olby *Origins of Mendelism*

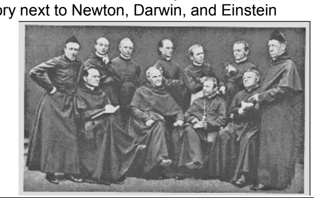
1761 - 1900

"The contrast between the two generations remained an enigma **until 1900** when Mendel's explanation was made generally known. Whereas Mendel explained the enigma on cytological and statistical grounds, Koelreuter explained it on bases which may be described as theological and alchemical. [He] looked upon the wonderful uniformity and exact intermediacy of F1 hybrids as evidences of Nature's perfection. The same cross repeated no matter how many times gave the same result. What caused the breakdown in the second generation? Surely, he reasoned, it must be man. Nature never intended that species should be crossed and to prevent it she had placed closely related forms far apart. Then came man mixing up nature's careful arrangement and cramming into the confines of his little garden species which formerly were separated by thousands of miles. … The strange motley of forms in the F2 generation was thus the direct result of tampering with nature."

R. Olby *Origins of Mendelism*

Johann "Gregor" Mendel

- Born to a peasant family in Brno (then Brunn) in Moravia
- Showed promise in school
- Studied at the University of Vienna, but could not get a degree, because of a psychiatric condition (exams made him nervous)
- Returned home, taught high school physics
- Became an abbot at a monastery – largely for financial reasons
- Bred peas for 8 years
- Presented the findings to his local "nature lovers" society
- Wrote to the leading authority of his time on plant hybridization, had his findings rejected as incorrect
- Died unknown, and remained so for 35 years
- Stands in history next to Newton, Darwin, and Einstein



Mendel's most famous words

Those who survey the work done in this department will arrive at the conviction that among all the numerous experiments made, not one has been carried out to such an extent and in such a way as to make it possible to determine the number of different forms under which the offspring of the hybrids appear, or to arrange these forms with certainty according to their separate generations, or definitely to ascertain their numerical relations to each other.

(note: thank you, Christian Doppler)

Wer die Arbeiten auf diesem Gebiete überblickt, wird zu der Ueberzeugung gelangen, dass unter den zahlreichen Versuchen keiner in dem Umfange und in der Weise durchgeführt ist, dass es möglich wäre, die Anzahl der verschiedenen Formen zu bestimmen, unter welchen die Nachkommen der Hybriden auftreten, dass man diese Formen mit Sicherheit in den einzelnen Generationen ordnen und die gegenseitigen numerischen Verhältnisse feststellen könnte.

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

Newton, Darwin, **Mendel**, Einstein

(i) The simplicity, clarity, elegance, rigor, and power of Mendel's experimental approach to the problem of heredity.
(ii) The influence of his work on subsequent development of science.

What is Mendel proposing to do?

1. Let's generate hybrids, and after having done so, determine, how **many different types** of children (progeny) appear in the crosses.
2. Let us do this analysis generation-by-generation, in other words, analyze the parents, their children, and their grandchildren SEPARATELY.
3. Let us DETERMINE THE RATIOS: if, in a given generation, there is more than one type of child, let us ask, **what proportion of the whole** each type is.

Scientific reductionism

Put together – intelligently – an experimental setup that "isolates" a particular component of a phenomenon for study. One attempts to "reduce" a problem to its simplest possible form.

All previous hybridists – including such titans as Carl Linnaeus, the first *Homo sapiens*, and Charles Darwin himself! – looked at the transmission through generations of **all** the traits for a given species, or multiple traits at once.

Why?

It requires indeed some courage to undertake a labor of such far–reaching extent; this appears, however, to be the only right way by which we can finally reach the solution of a question the **importance of which cannot be overestimated in connection with the narrative of how living beings develop.**

Es gehört allerdings einiger Muth dazu, sich einer so weit reichenden Arbeit zu unterziehen; indessen scheint es der einzig, richtige Weg zu sein, auf dem endlich die Lösung einer Frage erreicht werden kann, **welche für die Entwicklungs-Geschichte der organischen Formen von nicht zu unterschätzender Bedeutung ist.**

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

Astonishing foresight

One might ask – why did Mendel spend 8 corageous, lonely years in backbreaking, painstaking work, planting peas, dissecting their flowers, crosspolinating them, tracking their progeny, counting seeds, replanting those, etc etc?

The answer, in part, seems to be: he was convinced that he was studying not an obscure phenomenon in an irrelevant setting (seed color in peas). He thought he would discover a key mechanism that operates in all living things!

While he died in complete obscurity, his conviction proved entirely correct.

Words to live by

"The value and utility of any experiment are determined by the fitness of the material to the purpose for which it is used *, and thus in the case before us it cannot be immaterial what plants are subjected to experiment and in what manner such experiment is conducted."

*

Der Werth und die Geltung eines jeden Experimentes wird durch die Tauglichkeit der dazu benützten Hilfsmittel, sowie durch die zweckmässige Anwendung derselben bedingt. Auch in dem vorliegenden Falle kann es nicht gleichgiltig sein, welche Pflanzenarten als Träger der Versuche gewählt und in welcher Weise diese durchgeführt wurden.

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

A universally applicable statement

Will your experiment generate data that will be of any use?

Well, a key determining factor in that is whether you chose the right material to do the experiment with.

Is the object of your study optimally suited to answer the question you are interested in?

What plant to pick

"The selection of the plant group which shall serve for experiments of this kind must be made with all possible care if it be desired to avoid from the outset every risk of questionable results.

The experimental plants must necessarily:

1. Possess constant differentiating characteristics.
2. The hybrids of such plants must, during the flowering period, be protected from the influence of all foreign pollen, or be easily capable of such protection."

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

Useful piece of experimental guidance for a geneticist

"Accidental impregnation by foreign pollen, if it occurred during the experiments and were not recognized, would lead to entirely erroneous conclusions."

Experimental genetics – from Mendel's days and to this day – heavily relies on crosses. It is critical, therefore, that the cross be a controlled one, i.e., that it occur between specific organisms as per the experimental plan.

The problem, of course, is most organisms on Earth mate naturally, and uncontrollably.

A litmus test to determine, whether this class is right for you

Note: MCB140 is not an introductory genetics class, nor it is not a "fun" time spent discussing "cool" stuff about, like, DNA and gene "stuff."

- Bio 1 (or AP bio) – Mendel's laws, homozygous, heterozygous, dominant, recessive, mutation
- MCB – DNA, RNA, "central dogma of molecular biology"

→ If you cannot follow the story you are about to hear, do not take this class.

A lesson on how to get on the front page of the *New York Times*

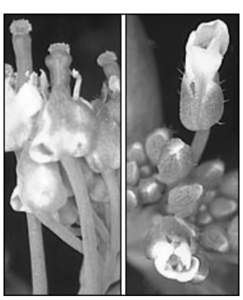
Nature, March 24, 2005: "Genome-wide non-mendelian inheritance of extra-genomic information in Arabidopsis" S. Lolle, R. Pruitt.

"*Arabidopsis* plants homozygous for recessive mutant alleles of the organ fusion gene HOTHEAD (HTH) can inherit allele-specific DNA sequence information that was not present in the chromosomal genome of their parents but was present in previous generations.

(in other words, hh plants, when crossed "to themselves," yield a surprisingly high frequency of Hh plants,)

"This previously undescribed process is shown to occur at all DNA sequence polymorphisms examined and therefore seems to be a general mechanism for extra-genomic inheritance of DNA sequence information. We postulate that these **genetic restoration events** are the result of a template-directed process that makes use of an **ancestral RNA-sequence cache**."

hh plant and its non-Mendelian offspring



"Startling Scientists, Plant Fixes Its Flawed Gene" – NYT 3/23/06

In a startling discovery, geneticists at Purdue University say they have found plants that possess a corrected version of a defective gene inherited from both their parents, as if some handy backup copy with the right version had been made in the grandparents' generation or earlier.

The finding implies that some organisms may contain a cryptic backup copy of their genome that bypasses the usual mechanisms of heredity. If confirmed, it would represent an unprecedented exception to the laws of inheritance discovered by Gregor Mendel in the 19th century. Equally surprising, the cryptic genome appears not to be made of DNA, the standard hereditary material.

Emphasis mine – fdu

Nature. 2006 Sep 28;443(7110):E8;

Plant genetics: increased outcrossing in hothead mutants. Peng P, Chan SW, Shah GA, **Jacobsen SE.**

Lolle et al. report that loss-of-function alleles of the HOTHEAD (HTH) gene in Arabidopsis thaliana are genetically unstable, giving rise to wild-type revertants. On the basis of the reversion of many other genetic markers in hth plants, they suggested a model in which a cache of extragenomic information could cause genes to revert to the genotype of previous generations. In our attempts to reproduce this phenomenon, we discovered that hth mutants show a marked tendency to outcross (unlike wild-type A. thaliana, which is almost exclusively self-fertilizing). Moreover, when hth plants are grown in isolation, their genetic inheritance is completely stable. These results may provide an alternative explanation for the genome wide non-mendelian inheritance reported by Lolle et al.

Initially, we constructed *hth-12 gl1-4* double-mutant plants in the Columbia ecotype, reasoning that *HTH* and *GL1* should revert independently because they are on different chromosomes. *hth-12* DNA carries a transfer-DNA (T-DNA) insertion (SALK_024611) and *gl1-4* is a guanine-to-adenine (G-to-A) transition mutation (like that shown previously to revert[1]) that changes the start codon of the trichome gene *GL1* (ref. 3) from ATG to ATA. Among 1,597 progeny of *hth-12 gl1-4* plants, 10 were phenotypically *GL1* (normal trichomes). Genotyping based on polymerase chain reaction showed that nine were heterozygous for *gl1-4*, and one was *GL1/GL1*. Surprisingly, the nine *GL1/gl1-4* plants were also heterozygous for *hth-12*, and the *GL1/GL1* homozygote was homozygous for *HTH*. These observations are most easily explained by pollen contamination (nine heterozygous plants) and seed contamination (one homozygous plant). We also found a single *hth-12* heterozygote that

The cross (a "self")_:

hh gg x hh gg

- Find 10 plants that are phenotypically G (i.e., "reverted" to wild-type).
- Genotype those.
- Observe that they are Gg (one allele "reverted").
- As a control, analyze the Hothead locus in those Gg plants.
- Remarkably, find that ALL of them are also Hh.
- Pull out Occam's razor.

I'm sorry, whose razor?

Occam's razor (also spelled Ockham's razor) is a principle attributed to the 14th-century English logician and Franciscan friar William of Ockham.

"All things being equal, the simplest solution tends to be the best one."

In other words, when multiple competing theories are equal in other respects, the principle recommends selecting the theory that introduces the fewest assumptions and postulates the fewest hypothetical entities.

Table 1 | Outcrossing in *hth* mutants

	Number of phenotypically revertant plants	
Genotype	Mixed population	Isolated population
hth-12	19/245 (7.8%)*	0/295 (0%)
hth-12	18/415 (4.3%)†	0/637 (0%)
hth-8	156/994 (15.7%)‡	0/890 (0%)§
hth-5	22/1144 (1.9%)‖	0/913 (0%)§

Homozygous *hth* plants were grown in a room with plants of mixed genotype (mixed population) or in isolation (isolated population). Progeny from these two populations were scored for plants with the wild-type *HTH* phenotype. (Plants were cared for by Yu Li, Shawn Cokus, Lynn Jacobsen, Zhongliang Peng and Suwen Wang. *BIN2-1::GFP* seeds were provided by Jianming Li.)

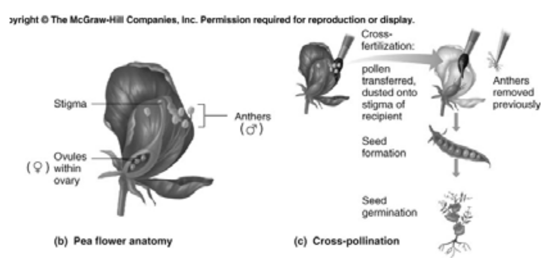
They should have listened to Mendel

"At the very outset special attention was devoted to the *Leguminosae* on account of their peculiar floral structure. Experiments which were made with several members of this family led to the result that the genus *Pisum* was found to possess the necessary qualifications.

Some thoroughly distinct forms of this genus possess characters which are constant, and easily and certainly recognizable, and when their hybrids are mutually crossed they yield perfectly fertile progeny.

Furthermore, **a disturbance through foreign pollen cannot easily occur**, since the fertilizing organs are closely packed inside the keel and the anthers burst within the bud, so that the stigma becomes covered with pollen even before the flower opens. This circumstance is especially important. As additional advantages worth mentioning, there may be cited the easy culture of these plants in the open ground and in pots, and also their relatively short period of growth. **Artificial fertilization is certainly a somewhat elaborate process, but nearly always succeeds.** For this purpose the bud is opened before it is perfectly developed, the keel is removed, and each stamen carefully extracted by means of forceps, after which the stigma can at once be dusted over with the foreign pollen."

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



The garden pea (*Pisum sativum*) – a powerful "model system" for genetic experimentation

1. Can cross, in an entirely investigator-specified fashion, two organisms of defined phenotypes.
2. Can also cross an organism "to itself" ("a self-cross") – "selfing."
3. "Invert the direction of the cross" (take male gametes from a plant carrying trait A, and fertilize an ovum from a plant carrying trait A' – and then do the inverse, i.e., male A' crossed to female A).

And now …

… to work!

Reading: Cobb review in *NRG*
Reading for next time: Ch. 2 in its entirety
Problem to do:
Section 2.1, problems 2 and 3

Questions

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