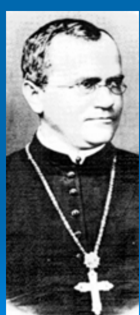
Genetics

Getting from one generation to the next

Gregor Johann Mendel



- 1822-1884
- Born in Austrian Silesia of a peasant family.
- Studied to become a science teacher at the University of Vienna.
- Became a monk in the Order of St. Thomas.

Mendel, the teacher

- As a monk, Mendel was assigned to teach general science at the Brünn Modern School.
  - He taught physics and chemistry to boys of about 12 or 13 years of age.
  - He had hoped to be a practicing scientist.

Mendel's Experiment

- From childhood Mendel had wanted to understand plant fertilization, in particular, how hybrids and varieties are produced.
- Around 1854, all on his own, Mendel undertook a long experiment on plant hybridization.
- The experiment took
  - 2 years to prepare.
  - 8 years to run.
  - 2 years to analyze the results.

Mendel's Experiment, 2

- As the experiment progressed, Mendel read all the existing scientific literature on theories of inheritance and he sought the views of scientists who were working on similar projects.
- He corresponded with Karl Nägeli, explaining his experiment and seeking Nägeli's views.
  - Nägeli replied to Mendel telling him his work was merely "empirical" rather than "rational."
  - Nägeli suggested that Mendel might instead like to help by doing some experiments for Nägeli.

Mendel's Scientific Career

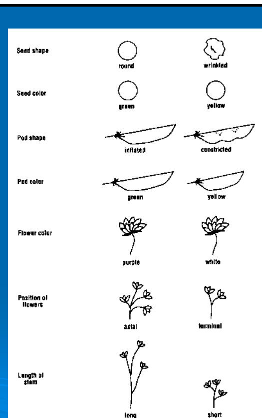
- In 1865 Mendel completed his work and presented the results at a meeting of his local scientific society, the Brünn Society for the Study of Natural Science.
- In the following year, 1866, Mendel revised the paper and it was published in the journal of the Brünn Society.
  - Though an obscure society, its journal was carried by major scientific libraries across Europe. As well Mendel sent offprints of his paper to several prominent botanists.
  - There is no record of anyone having taken Mendel's work seriously in his lifetime.

Mendel's Scientific Career, 2

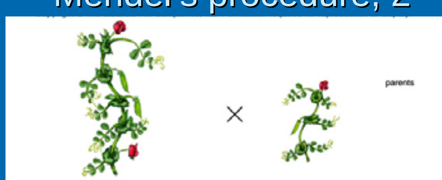
- In 1868, the Abbot of the monastery died and Mendel was elected to replace him. Mendel spent the rest of his life in administrative work, completely putting his scientific work behind him.
- In 1884 Mendel died, unknown as a scientist.

Mendel's procedure

- Mendel chose to study the common garden pea plant, which had several varying characteristics.
- Mendel had discovered that there were 7 pairs of characteristics that were sharply differentiated and easily identified.
  - Each individual plant showed one of each pair of characteristics, but they appeared in any combination.



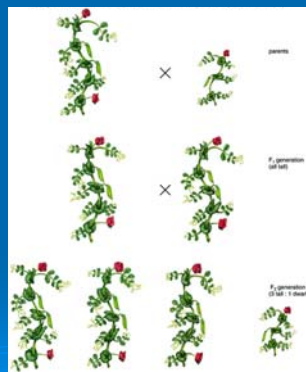
Mendel's procedure, 2



- He bred successive generations of his plants until he had separate groups that each bred "true" for each trait.
  - E.g., all *talls* in one group and all *shorts* in another, etc.
- Then, he fertilized flowers from one group with pollen from the group with the opposite trait, and recorded the characteristics of the offspring.

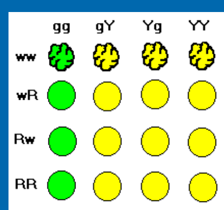
Mendel's procedure, 3

- In the first generation all plants exhibited the same characteristics.
- But when he inbred this generation he found the emerging pattern of a 3 to 1 ratio of the traits on the left to those on the right.



Mendel's procedure, 4

- He continued for many generations and combinations of generations before drawing his conclusions.
  - At right, results of breeding together plants with two different pairs of characteristics, here *round* versus *wrinkled* and *green* versus *yellow.*



Resulting ratios of the combination: 1 green & wrinkled, 3 green & round, 3 yellow & wrinkled, and 9 yellow & round.

Mendel's Laws

- *The Principle of Segregation* – In the formation of the sex cells of the plants, pairs of factors separate. One of each pair remains in the sex cells.
- *The Principle of Independent Assortment* – The characteristics he identified can all be inherited independently of each other in any combination.
- *The Law of Dominance* – Each characteristic is inherited independently due to the interaction of two "factors" – one from each parent. One of the factors always predominates over the other.

Characteristics of Mendel's Results

- Mendel applied mathematical analysis to biology – something virtually never done before.
- Mendel found that inheritable characteristics occur in fixed ratios in a population.
- Mendel's work implied that inheritance has a discrete structure, since there never was any blending of characteristics.

A problem from Darwin's theory of evolution

- How could a slightly favourable characteristic possibly be passed on in a population long enough to be naturally selected without being washed out back to the mean of the population?
  - Answer: the inheritable characteristic is carried in a discrete, discontinuous form that remains undiluted.

Mendel's eventual recognition

- In 1900, three biologists, de Vries, Correns, and Tschermak all came to the conclusion that particulate, discrete inheritable traits was necessarily haw nature must be organized.
  - They each began a search of the scientific literature to see if anyone had done any experimental work that would help to confirm this view.
- They each independently and at about the same time discovered Mendel's 1866 paper, and realized that Mendel had not only done relevant work, but figured out the general structure of inheritance.

Mendel's "Factors"

- Mendel identified the existence of factors responsible for individual inheritable traits, but not what they were in any physical sense.
- Work on chromosomes led scientists to believe that these factors were conveyed by the chromosomes , but how was not known.

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The Gene

- To facilitate the search for the physical thing that would carry the inheritable factors, a term was coined, the *gene.*
  - The gene was conceived to be the unit, the "atom" of heredity.
- Finding the gene would be a major activity of experimental biology in the 20th century.

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Thomas Hunt Morgan

  - 1866 – 1945
- Working at Columbia University in New York.
  - Trained almost all of the major geneticists of the early 20th century.
- Morgan did similar experiments to those of Mendel, but instead of peas, he used the ordinary fruit fly, *Drosophila melanogaster.*

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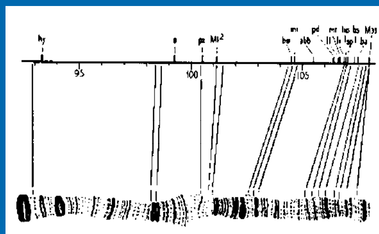
The Search for the Gene



- Morgan was able to establish that whatever genes are, they are represented in a linear order on the chromosomes.

Genes and Mendel

- Mendel's factors fit well with the idea that genes are somehow locations on the chromosomes.
- The presence of genes on *pairs* of chromosomes – one from each parent – corresponded with Mendel's factors.

Linkage

- Contrary to what Mendel thought, some characteristics are not independent of each other. They may always appear linked to other characteristics.
- At right, sex-linked eye colour in fruit flies. All white-eyed flies are necessarily male.

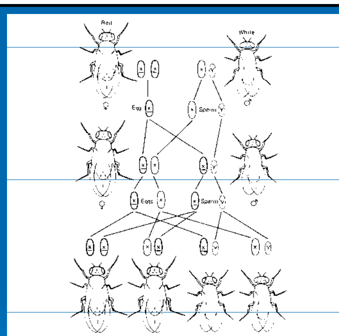


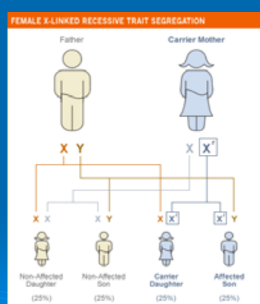
Fig. 6.4.2 Sex-linked inheritance in *Drosophila*. A white-eyed male (right) is crossed with a normal, red-eyed female (left). The first generation are all red-eyed but in the second generation one out of every four flies is white-eyed and male. In 1910 Morgan explained this by assuming that some X-chromosomes (shaded in diagram) contained the gene for red eyes while other X-chromosomes contained the white-eyed gene.

Sex-linked heritable diseases

- Some diseases that tend to run in families have been found to be linked to the X-chromosome.
- A famous example is hemophilia, which was unusually common in the family of Queen Victoria.

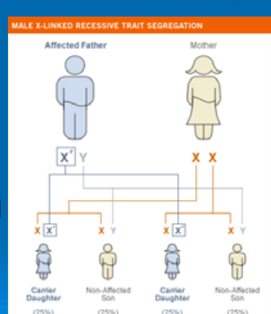
Sex-linked heritable diseases, 2

- Hemophilia is carried by a defective X chromosome, and is a recessive trait.
- Since women have two X chromosomes, they rarely suffer from the disease, but often are carriers of it.



Sex-linked heritable diseases, 3

- Men, on the other hand, have only one X chromosome, so if theirs is defective, they will suffer from hemophilia.
- All their daughters will be carriers of the disease.



Genes and Darwin

- Mendelian traits form a fixed set of factors that produce a finite set of variations.
  - No new variations would arise, just different combinations of the same ones.
  - How was evolution possible if Mendel's conception was correct?
  - Darwin required that subsequent generations of a species exhibit a set of characteristics that varied, but around a different center.
    - Answer: Mutations.

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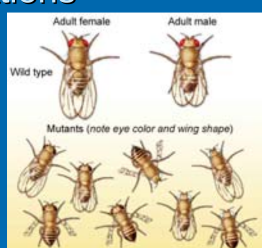
Mutations

- Morgan's team induced genetic changes in the chromosomes of their fruit flies by exposing them to radiation, and other means.
- These produced changes – mutations – in the offspring that were not normal variations.



The induced mutations were usually harmful, often fatal, but they also could be changes that would be beneficial. Thus mutations provide a possible path for evolution with natural selection.

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Genes as Coded Information

- Max Delbrück, physicist and former student of Niels Bohr, became interested in studying life processes with the eye of a physicist.
- In 1935 he wrote a paper, "On the nature of gene mutation and gene structure" in which he suggested that if the genes conveyed information to the body, it had to be via the arrangement of the individual molecules of the gene.

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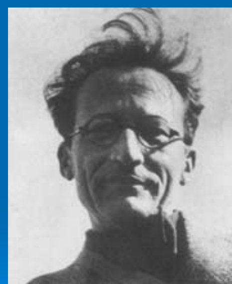
Genes as Coded Information, 2

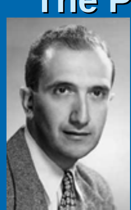
- The same idea occurred to another physicist, this one being one of the top physicists of the day, Erwin Schrödinger.
  - Schrödinger wrote a similar analysis in a short book called simply, *What is Life?* in 1944.

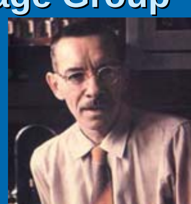


Phages

- Delbrück decided to give up physics for biology and went to do post-doctoral work at the California Institute of Technology on *phages* (bacterial viruses).
  - Phages are among the simplest life forms and can be studied at a much more fundamental level than either pea plants or fruit flies.

The Phage Group





- Delbrück met Salvador Luria and Alfred Hershey, who were both interested in the work on phages.
- Together they formed the Phage Group in 1943, to study the nature of the gene, via research on phages and similar organisms.

Converging sciences

- The search for the gene transcended the boundaries of a single science subject and a single method of research.
- Success in finding the gene came from the convergence of several disciplines, mainly:
  - Cell Biology and Heredity Research
  - Organic Chemistry
  - Physical Chemistry
  - Physics

The Heredity Problem

- Cell biology had identified the importance of the sperm and egg cells.
  - The nucleus of the sperm cell joined with the nucleus of the egg in fertilization.
  - The process of cell division was studied carefully.
  - Chromosomes were identified and tracked through cell division and fertilization processes.
  - Everything pointed to the cell nucleus as the location of activity.
- Mendel and Morgan and others established that the gene must be a discrete entity, located on the chromosomes

Organic Chemistry

- "Animal Heat"
  - Since Aristotle, it had been noted that animals (warm-blooded animals, anyway) produce heat when they are alive.
    - This was a mystery awaiting an explanation, which came from organic chemistry.
  - Heat is produced by exothermic chemical reactions in the cells.
    - This is the function that Schwann named *metabolism*.
- Conclusion: The important chemical life processes, must occur in the cells.

Physical Chemistry

- Bohr's model of the atom with its electron shells helped picture how molecules were arranged and held together.
  - The actual shape of a molecule was seen to be a major factor in what compounds it would form.
  - A new branch of chemistry emerged, *physical chemistry*, that used the tools of quantum mechanics to determine the shape, strength, and configuration of chemical bonds.

Physics

- X-rays as a research tool.
  - Materials that formed crystals when they solidified could be studied by bouncing x-rays off them and analyzing the pattern of shadows cast.
- This became a new specialty called *crystallography*, which used what are called x-ray diffraction techniques to produce pictures of molecules.
  - Knowing the actual 3-dimensional configuration of a molecule can help explain how it works.
  - If genes are actually molecular structures, this would be most useful information.

The Rise of the Multidisciplinary Laboratory

- Multi-disciplinary laboratories began to be established.
  - They would collect people from a variety of different areas of expertise, put them together, and set them to solve some of the difficult intractable problems.
- One of the best was the Cavendish Laboratories at Cambridge University.
  - Among the hot problems being looked at in the early 1950s at its Medical Research Division was DNA.


The Cavendish Laboratories