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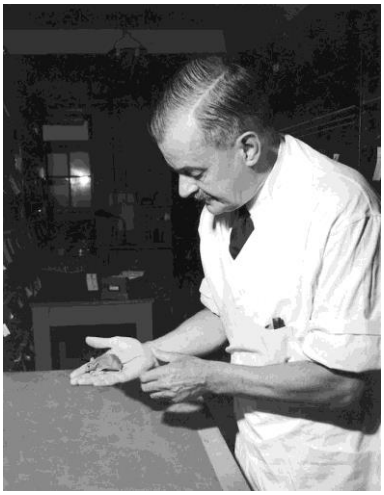
From Mendelian inheritance to molecular genomics: a brief appreciation of genetics

by Tim Nguyen

**Mendel's peas and mice.** Biology shares its own evolution in thinking, from mystical elements and temperature determining the sex of a newborn baby to analyzing strange organisms nearly naked to the invisible eye. Genetics, a now cornerstone of all biology, has ventured into making fantastical musings a feasible reality. The prospect of some invisible force governing inheritance has been speculated throughout various civilizations despite its mystery to many philosophers, but its modernity comes in the humble form of a monk in Austria.

Gregor Mendel was known for discovering the ability of peas to inherit certain traits, called phenotypes (e.g. color), from its parents in a statistical manner (and also for initially using mice to observe inheritance before his bishop insisted on him keeping his sense of propriety by not keeping mice in his bedroom). However, geneticists in the early 20th century picked up Mendel's fascination with genetics and applied it to basic biological questions and human diseases.

**Fashion industry in biology.** Model systems are a means to answer questions in topics such as genetics, and they are frequently being discovered and modified. Model systems are generally low maintenance, relatively cheap, and able to create large sample sizes (the more numbers you had, the better your findings are) in short amount of times. After Mendel developed ideas for inheritance in his model of peas, others were eager to expand on his ideas.

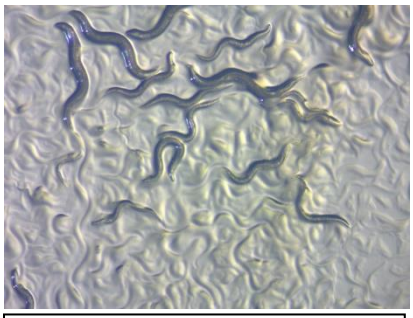


Dr. Little was one of the pioneers of mice genetics and founded the Jackson Laboratory, now a leader in providing mice strains for researchers around the globe. **Credit: The Jackson Laboratory**, https://www.jax.org/research-and-faculty/research-centers/the-jackson-laboratory-cancer-center/history-of-the-cancer-center

Early genetic models established included Drs. Little and Morgan use of inbred strains of mice and fruit flies (*Drosophila*) to study the inheritance of disease and general phenotypes, respectively. What makes inbred strains so powerful is its ability to allow researchers to make direct comparisons between distinct features. For example, Dr. Little wanted to uncover the inheritance of cancer, so he mated (crossed) a mouse population that are generally healthy with another distinct population that was known to develop tumors. By crossing the mice, Dr. Little observed the persistence or disappearance of cancer from each generation. Dr. Morgan used a similar concept by crossing Drosophila strains to discover that some traits like eye color are sexually linked (a trait being on the X or Y chromosome).

These scenarios show the power of forward genetics, which is finding the genetic details, or genotype, of a phenotype.

**The genesis of biotechnology.** The field of genetics was expanded by the discovery of Rosalind Franklin's work in X-ray crystallography (a form of molecule photography) showing the helical structure of deoxyribonucleic acid (DNA), Drs. Meselson and Stahl's work on showing how DNA replicates in a semiconservative fashion (every DNA strand is a template strand for the new strand of DNA being formed). From this basis, technology to amplify and visualize DNA was developed and by scientists like Dr. Mullis, and gene manipulation technology shown by Drs. Mello and Fire in the roundworm *C. elegans* called RNA



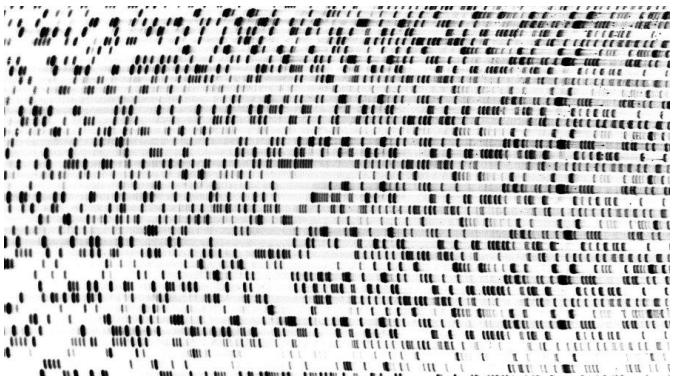
*C. elegans*, a little roundworm, is a model system used to study the genetics of development and neurobiology. Drs. Mello and Fire showed RNAi to be a useful technology using these worms. Here, they are feeding on *E. coli* bacteria.
**Credit:** http://genestogenomes.org/the-tiny-worm-with-a-big-impact/

interference (RNAi). Gene manipulation, such as silencing or over-expressing it allowed scientists to find the purpose of a gene and see the phenotypic consequences of the genetic change. This concept is known as reverse genetics.

Altogether with more developments in biological processes and systems to study specific components of health and society, genetics as a technological asset was established as a biological field involved in the dawn of medical therapies, agricultural production increases, and environmental sustainability.

**All the A's and T's and C's and G's.** Near the turn of the millennium, genetics has become a mainstay tool for biology. However, one roadblock in research remained: the analysis of biological systems such as humans, crops, and other animals remained incomplete. Genes studied by scientists around the world for decades are only very small fraction of the bigger picture. In fact, it turns out genes comprise less than a quarter of all the DNA in each cell, and the only way to understand how processes operate in any living system is to look at the bigger picture—taking a genomic approach.

Scientists worldwide knew that to do this, they had to find a way to sequence and annotate the species' genome: millions and millions of A's, T's, C's, and G's in each cell that provide information for how a living organism should move, grow, and reproduce. With government funding agencies from multiple countries and private institutions independently on board, a >$3 million, 15-year effort called the Human Genome Project began in the late 1980s to create the first draft of the human genome alongside some other established model systems like mice, *C. elegans*, and *Drosophila melanogaster*.



During the Human Genome Project, DNA sequencing was done by a few approaches. One was Sanger Sequencing, a method developed in 1977 where samples of DNA are replicated using radioactively modified bases to synthesize different sizes of DNA, and the letters were read as bands on a gel.
**Credit:** https://www.yourgenome.org/stories/the-dawn-of-dna-sequencing

The task was feared to be daunting and hopeless at many points during the global effort, but with the eventual collaboration between government and company efforts and creation of millions of black lines on thousands of gels, the first human genome sequence and annotation draft was completed and published.

**CRISPR and the next generations.** The prospect of sequencing 3 billion letters more effectively and less expensively was inevitable. Within a decade after the Human Genome Project, the cost of sequencing reduced from millions of dollars to approximately $1,000—this number is still decreasing rapidly. With the rapid availability of sequencing through higher computational power and accessible reagents, this efficient technology, dubbed next-generation sequencing, scientists could more quickly sequence their samples and characterize their genes at a global, or transcriptomic, level. It was only fitting that the ability to look a cell's whole genome was paired with an advancement in genetic manipulation.

Clustered regularly interspaced short palindromic repeats, or CRISPR, was discovered as a bacteria's adaptive immune system against viruses, and fitting characterized while the human genome was

being put together. The CRISPR system is a library of short DNA molecules from viral infections the bacteria previous survived from, and if the same virus tries to infect the bacteria, the DNA gets transcribed to an RNA molecule that acts as a guide (gRNA) for bacterial scissors called Cas9. The gRNA-Cas9 complex goes around the bacteria's genome and if any DNA matches up with the gRNA perfectly, the Cas9 cuts the section out, deleting the virus.

Poetically, scientists in the early 2010s found a way to harness it as a genetic tool to make precise and effective edits, rivaling and complementing the established RNAi system developed years earlier. Using variations of CRISPR, ways to change a single mutation or even deleting out whole sections of DNA—thousands of bases—have been shown with great effect. The promise of precise editing with CRISPR-Cas9 with next-generation sequencing allowed the field of genetics to explode to great proportions, making studies of the genetic underpinnings of complex diseases, human ancestry, agricultural yields, and ecological studies vastly fast—perhaps, too quick for our own good.

**Where we go from here: concluding remarks**. New methods of forward genetics such as genome-wide association studies (GWASs) have proven to be powerful tools that utilize the littlest details of genetic variation found in individuals, called single nucleotide polymorphisms (SNPs) to identify initially hidden variations associated with rare diseases, something that has not been done effectively before. Reverse genetics is augmented with the use of CRISPR-based editing that allows geneticists to have confidence with their genetic manipulations. Studies of genes are growing to be more global, taking into consideration of the cell, tissue, organ, and whole living being. The essence of genetics remains and is now on the cusp of being fully realized. In the light of health, the power of information from patient sequencing has allowed promise for precision medicine, but what remains to be seen is how transparent information can be between geneticists, physicians, patients, and people simply interested in genetics.

Lastly, there has been a huge boom in direct-to-consumer (DTC) DNA testing. The boost of biology awareness and knowledge has been bolstered by greater education at all levels and through a great demand for science outreach to the public. Genetics is now on the radar of consumers who are curious about how genetics may show them their genealogy and who they biologically are. However, the implications of DTC testing remain uncertain as federal regulation will inevitably be placed on what can be disclosed in the testing kits, as consumers may think that DTC tests can replace more expensive clinical tests relating to disease risks. That is where genetic counselors and science communicators come into play to mediate dialogue between genetics and people.

Nevertheless, the future and application of genetics is bright. Its implication for health progression globally and broadening the knowledge of other living systems beyond humans is only within reach compared to the days when complex diseases and visualizing DNA was more fantastical.

I believe no geneticist envisioned A's, T's, C's, and G's to receive great interest and support from communities outside medicine, pharmaceuticals, and academic institutions. The most baffling truth I realized is how little I reflected in the field. I barely scratched the surface, and I do not think anyone can cover every exciting advancement in a single piece of writing.

From peas grown in a monastery to libraries of DNA sequences ready to be used to aid in curing complex diseases, I can only wonder, with eager anticipation, how much genetics will expand beyond my own comprehension.

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