Biotechnology: Crash Course History of Science #40

Crash Course: History of Science
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[Intro]
As some scientists worked to control life at the scale of global agriculture, others worked in a different direction. The mid-1900s was a period of reexamination of one of our big questions: **what, exactly, is life?** Let's talk about DNA and biotech!

[Main Video]
Although the story is complex, it's often simplified to one big "discovery" of DNA made in 1953 by two dudes who won Nobels. Turns out, there were *also* other people involved.

By the 1940s, researchers knew that the cell nucleus contained thread-shaped structures called chromosomes that played a critical role in cell division. Chromosomes seemed to be made of a mixture of protein and *other stuff.* And this other *key* stuff was a molecule made out of **carbon**, **hydrogen**, **nitrogen**, and **phosphorus**. This was **deoxyribonucleic acid**, or **DNA**.

Isolated, DNA looks kind of like a white powder, but no one knew DNA's structure. A molecule's structure-- the way it fits together-- tells us about how it works and *maybe* how to redesign it.

In 1944, Austrian physicist **Erwin Schrödinger**-- yeah, the cat guy-- published a short book called *What is Life?* reviewing this deceptively simple question. Scientists knew that there must be a unit of heredity, the "**gene**", that must be part of the chromosome. Schrödinger examined the laws of physics, determining that the gene must be very small-- only a few thousand atoms in size. It must vary, yet it must be orderly, and not give rise to too many mutations.

So Schrödinger threw down the challenge: how does this gene physically encode the information that defines life? He argued that this was among the most interesting questions facing science. And he suggested that one of the people best poised to answer it was biophysicist **Max Delbrück**.

Delbrück ran a loosely organized network of researchers at Cold Spring Harbor Laboratory Caltech and elsewhere, called the **Phage Group**. The Group worked with viruses that parasite bacteria, called **bacteriophages.** Viruses are just nucleic acids in little protein robot-bodies.

***The Phage Group* did important work on how life works at a small scale, using *radioactive tracers* inside viruses. But even they couldn't tell if it was the *DNA* part or the *protein* part of the *virus* that took over the *bacterium*.**

And no one could explain how *either* physically encoded information. So by 1950, the pressure to understand DNA was on even though not everyone was convinced that DNA was the physical substrate of heredity at all! Despite this uncertainty, scientists set out to *win this race*.

The most famous was American chemist Linus Pauling who went on to join the short list of people with *two* Nobel Prizes. Pauling was an obvious choice because in 1951, he characterized the **alpha helix** structure of common proteins. He used an empirical approach, **X-ray crystallography**. X-rays, which have wavelengths much smaller than visible light, pierce molecules then scatter, making a diffraction pattern that reveals information about the molecule's shape.

Crystallography is an incredibly finicky technique. But Pauling correctly showed how common proteins fold up into elegant little spirals. He then decided to tackle DNA, guessing *incorrectly* that it was made up of *three* helices.

Also in the race was **James Watson**-- a brilliant, young, and brash American biochemist. "Brash", of course, being the historian's euphemism for "sexist jerk." He was a member of the Phage Group and a fan of Schrödinger's *What is Life?* Watson traveled to the University of Cabridge's Cavendish Laboratory. There, he partnered with English biophysicist **Francis Crick**, who became one of the great theorists of modern biology.

Watson and Crick's approach was *modeling* DNA-- asking which *atoms* went where, based on the laws of *chemistry* and *physics*. Now if you've read Watson's best-selling autobiography, *The Double Helix*, you'd think he and Crick did the heavy lifting in discovering the structure of DNA. You wouldn't know that Harvard University Press *refused* to publish his book because of its potentially libelous characterization of their collaborators!

ThoughtBubble, show us another side of the story!

Watson cast English chemist Rosalind Franklin as the villain. Franklin worked at King's College London, not the Cavendish, and she was Jewish, and she was...also...a woman. She also went to a talk by Watson and Crick and tore apart their suggested model of DNA. **The head of the Cavendish was humiliated, forbidding them from more DNA-modelling.**

You see, Franklin was a leading expert in X-ray crystallography. Her photographs had shown that there were two forms of DNA: **A**, which is dry and crystalline, and **B**, which is wet-- how DNA looks in living cells. This discovery was a fundamental step in understanding DNA. (We now know that there is a third form: **Z**-DNA).

Then in 1952, Franklin made one of the most famous photographs in science: Photo 51. It shows a clear "X" pattern-- the signature of a helix, or spiral-stair shape. **But Franklin didn't know that the Deputy Director of her lab, Maurice Wilkins, was secretly passing her notes and images to Watson and Crick. The rest became history...**

In 1953-- working on their model, reviewing facts about the four nucleic acids in DNA, or bases, and looking at Franklin's images-- Watson and Crick realized DNA must be a double helix. And that the bases must be paired so that the A's equal the T's and the G's match the C's. **The zipper shape of the double helix allows DNA to transmit information from generation to generation with few copying errors.**

A cellular machine "unzips" the staircase down the middle, and figures out one half of a base pair by looking at the other. If one base is an A, it must connect to a T. Simple!

Watson and Crick invited Franklin to Cambridge to review their work. She immediately acknowledged that it was correct. She just didn't know how much they had relied on her own work! **Thanks, Thought Bubble.**

After publishing their model and the data backing it up, Watson and Crick became scientific celebrities. Franklin, however, died prematurely of cancer, likely due to her work with X-rays. And the Nobel Prize is *not* awarded posthumously. So in 1962, Watson, Crick, and Wilkins shared the Nobel without acknowledging the debt they owed to Franklin.

But, in part, because Watson described Franklin so horribly in his book-- he called Franklin "*Wilkin's assistant*"-- historians went back and researched her life, writing her back into the role of protagonist in the story of DNA.

So a scientific object like DNA is assembled out of other scientific objects such as X-ray images, textbooks, and three-dimensional models of tin and cardboard-- but also erroneous ideas such as

Pauling's triple helix, as well as relationships, and competitive drives for fame. With DNA revealed, life itself could theoretically now be not only "read" but "programmed." Remember, this was around the same time as the birth of computing!

So **DNA became a *machine-language* "program" to make *RNA*, which became an *assembly-language* "program" for making *proteins*, which are what life is made out of. This process was thought to be quite *computer-like* moving only in one direction--from DNA to RNA to proteins.**

This rule, first expressed by Crick, is the **Central Dogma of Genetics**. We now know it's more complicated, but the essential idea is useful.

The question after 1953 was another "how" about the genetic code. DNA has four nucleic acid "letters"-- A, T, G, and C, with a U instead of a T in RNA. But how do these code for the twenty amino-acid "letters" of the proteins that we're made out of. Some of the DNA discoverers went back to the theoretical drawing board.

In 1954, Watson and Soviet-American physicist George Gamow founded the "RNA Tie Club" to figure it out. And Gamow, Crick, and others did important theoretical work. But in 1961, biochemists Marshall Nirenberg and Heinrich Matthaei cracked the first piece of the code. And over the 1960s, other biochemists worked to figure out the rest, including how RNA works.

Also **in 1953, University of Chicago chemist *Stanley Miller* and his advisor *Harold Urey* produced *amino acids*, the building blocks of life, out of an electrified broth of not-living nutrients.**

The Miller-Urey experiment supported the idea that all life on earth arose in a primordial soup of basic nutrients billions of years ago. Some scientists though-- including Crick-- found this unlikely and thought life on earth probably came from outer space, an idea called **panspermia**.

The discoveries of 1953 marked a new era in biology. Evolution now had a molecular basis: mutations are copy errors in DNA-- rare, but inevitable. Mutation give rise to the variation that Darwin and Wallace described.

***Molecular* techniques revolutionized the study of *evolution*. Species were regrouped by the similarity of their *DNA*, not their visible physical features.**

Crabs, for example, evolved several times, millions of years apart. It turns out that having armor-like skin, and claw hands, and being able to digest *literal trash* is super useful in all kinds of different watery environments!

Another use of the newly deciphered genetic code was industrial. Arguably, biotechnology had been around for a while. Beer, after all, is made using engineered strains of brewers' yeast. But this process takes a long time and involves **strain selection**, or picking types of yeast with useful properties-- not molecular-scale editing.

After 1953, scientists started looking for genes connected to traits of interest. The problem was knowing what genes code for what traits wasn't useful without having a way to move those genes around.

So biotech took off in the early 1970s in San Francisco, after Paul Berg, Stanley Cohen, and Herbert Boyer published the results of experiments with **recombinant DNA** or **rDNA**-- new, synthetic sections of DNA made by cloning sections from one organism's genome into another. With rDNA, scientists could splice sequences of DNA. Berg became the first person to join DNA from two different species in one microbe.

rDNA allowed scientists to copy the genes involved in the creation of the very important hormone insulin, which regulates how much sugar the body has in its bloodstream, into bacteria and yeast. Before rDNA, people with diabetes had to get insulin from pigs or other animals, but synthetic insulin is more pure. Industrial genetic engineering exploded.

In 1980, the Supreme Court of the United States heard a landmark case called Diamond v. Chakrabarty. The question was whether or not a company could patent a bioengineered life form-- a microbe designed to eat up spilled oil. SCOTUS said yes: **if you *engineer* an organism's *genome*, then it becomes a *technology***.

And by 1980, the biotech industry also had its first initial public offerings, or IPOs, where shares of a company become available on a stock market. Several companies launched with *massive* valuations. And universities-- especially around San Francisco and Boston-- began to view their scientific discoveries as major sources of money. They set up offices of technology transfer or licensing. Scientific knowledge-- and life itself-- became potential technologies.

Next time, we'll gonna look at how biological technologies changed medicine and agriculture. It's time for the birth of Big Pharma, GMOs, and IVF.

[Outro]
Crash Course History of Science is filmed in the Dr. Cheryl C. Kinney Studio in Missoula, Montana and it's made with the help of all these nice people. And our animation team is Thought Café.

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