AFD Ep 418 Links and Notes - Fermentation, Biotechnology, and Penicillin [Bill/Rachel] - Recording Mar 20, 2022

- https://en.wikipedia.org/wiki/History_of_biotechnology
    - Earliest form of biotechnology is zymotechnology, which is the use of technology to improve beer brewing techniques. These techniques were applied more broadly to improve agriculture and prevent famine and malnutrition. Although brewing today is a wide and varied field filled with international megacorporations down to nanobreweries, it held great economic power in the late 19th Century. In Germany, beer contributed as much to GNP as steel, and taxes on alcohol were an important source of government revenue, so improvements in brewing were economically significant. An industry of consultants sprung up to advise brewers on how they could reap these technological benefits. *The most famous was the private Carlsberg Institute, founded in 1875, which employed Emil Christian Hansen, who pioneered the pure yeast process for the reliable production of consistent beer. Less well known were private consultancies that advised the brewing industry. One of these, the Zymotechnic Institute, was established in Chicago by the German-born chemist John Ewald Siebel.*
    - *The heyday and expansion of zymotechnology came in World War I in response to industrial needs to support the war. Max Delbrück grew yeast on an immense scale during the war to meet 60 percent of Germany's animal feed needs.Compounds of another fermentation product, lactic acid, made up for a lack of hydraulic fluid, glycerol. On the Allied side the Russian chemist Chaim Weizmann used starch to eliminate Britain's shortage of acetone, a key raw material for cordite, by fermenting maize to acetone. The industrial potential of fermentation was outgrowing its traditional home in brewing, and "zymotechnology" soon gave way to "biotechnology."*
    - *Fermentation-based processes generated products of ever-growing utility. In the 1940s, penicillin was the most dramatic. While it was discovered in England, it was produced industrially in the U.S. using a deep fermentation process originally developed in Peoria, Illinois. The enormous profits and the public expectations penicillin engendered caused a radical shift in the standing of the pharmaceutical industry. Doctors used the phrase "miracle drug", and the historian of its wartime use, David Adams, has suggested that to the public penicillin represented the perfect health that went together with the car and the dream house of wartime American advertising. Beginning in the 1950s, fermentation technology also became advanced enough to produce steroids on industrially significant scales. Of particular importance was the improved semisynthesis of cortisone which simplified the old 31 step synthesis to 11 steps. This advance was estimated to reduce the cost of the drug by 70%, making the medicine inexpensive and available.*
    - Genetic engineering - Modern biotechnology was born in 1953, when Watson and Crick described the structure of DNA (based on research by Rosalind Franklin!) Another major breakthrough was the 1973 discovery by Cohen and Boyer of a recombinant DNA technique by which a section of DNA was cut from the plasmid (a small molecule of DNA separate from chromosomal DNA) of an *E. coli* bacterium and transferred into the DNA of another. This approach could, in principle, enable bacteria to adopt the genes and produce proteins of other organisms, including humans. This recombinant DNA technique was used to synthesize human insulin in bacteria in the first pharmaceutical application of this technology. In 1978, the University of California patented the gene that produces

human growth hormone, thus introducing the legal principle that genes can be patented.
    - *However, a 2013 Supreme Court case, Association for Molecular Pathology v. Myriad Genetics, Inc., ruled that human genes cannot be patented in the U.S. because DNA is a "product of nature." The Court decided that because nothing new is created when discovering a gene, there is no intellectual property to protect, so patents cannot be granted. Prior to this ruling, more than 4,300 human genes were patented. The Supreme Court's decision invalidated those gene patents, making the genes accessible for research and for commercial genetic testing.*
      The Supreme Court's ruling did allow that DNA manipulated in a lab is eligible to be patented because DNA sequences altered by humans are not found in nature. The Court specifically mentioned the ability to patent a type of DNA known as complementary DNA (cDNA). This synthetic DNA is produced from the molecule that serves as the instructions for making proteins (called messenger RNA).
      https://medlineplus.gov/genetics/understanding/testing/genepatents/
    - [in the notes but not the show] A very broad history of biotechnology from pre-industrial to industrial processes (how crazy is it that the auto industry used fermentation for paint thinner?!):
      https://www.lonestar.edu/history-of-biotechnology.htm
- US agriculture:
  https://www.fda.gov/food/agricultural-biotechnology/science-and-history-gmos-and-other-food-modification-processes
    - Although agricultural food modification has been happening since the dawn of civilization, genetic engineering has allowed food science to accelerate. Prior to the genetic engineering era, modifying food plants and animals was a slow and arduous process of selective breeding and hoping that the results were beneficial to yields and hardiness. As most of us learned in high-school biology, Gregor Mendel, a monk with a pea-breeding hobby, discovered that traits from his peas were passed down from generation to generation, and he was able to demonstrate the basics of genetics. In 1940, before the structure of DNA was even discovered, plant breeders used radiation or chemicals to randomly alter an organism's DNA, which sounds like an origin story for a comic book character. After Cohen and Boyer's recombinant DNA breakthrough, a whole new world of agricultural food production opened up. But people were leery of genetically modified foods and how they might affect people who ate them. To regulate safety standards of genetically engineered foods, the federal government established the Coordinated Framework for the Regulation of Biotechnology in 1986. This policy describes how the U.S. Food and Drug Administration (FDA), U.S. Environmental Protection Agency (EPA), and U.S. Department of Agriculture (USDA) work together to regulate the safety of GMOs. In 1994, the first GMO produce - a tomato - hit market shelves after it proved to be just as safe as traditionally-bred tomatoes. In 2015, the FDA approved an application for the first genetically modified food animal, a GMO salmon. And, in recent news, the FDA completed consultation on the first food from a genome edited plant.
    - This site also goes through the process of developing a GMO plant - in this case Bt corn - from concept to market. First, a gene is found that confers a desirable trait. Bacillus thuringiensis is a soil bacterium that creates a natural insecticide. Bt has been used as an insecticide for many years in organic agriculture. Scientists isolated the gene that creates the insecticide, then copied it. They then insert the gene into the DNA of the corn plant. The corn's other genes are unaltered. Then

scientists grow the new Bt corn, first in laboratories, then in test fields, until they are sure the corn exhibits the desired insect resistance and that the corn is safe to consume. This process takes years to review before it's made available to farmers.

- Synthetic insulin and capitalism at the origin point:
    - https://www.smithsonianmag.com/smithsonian-institution/a-history-of-biotechnology-in-seven-objects-180947559/
        - Prior to 1982, diabetics got their insulin extracted from cow or pig pancreases. Prices and supply varied based on meat prices, and it was feared that the supply wouldn't be able to keep up with increasing numbers of diabetics. Humulin, the first pharmaceutical application of recombinant DNA technology, changed the world.
        - *One of their first achievements was synthetically building the human insulin gene in the lab, a single genetic base pair at a time. In order to check the accuracy of their sequence, they used a technique called gel electrophoresis, in which electricity forces the DNA through a gel. Because larger pieces of DNA migrate more slowly than smaller pieces, the process effectively filters the genetic material by size, allowing researchers to pick out the pieces they want, one of the key steps in early genetic sequencing methods.*
        - *Electrophoresis is still widely used, but the equipment donated by Genentech is decidedly more improvised than the standard setups seen in labs today. "You can see it's sort of made by hand," says Mallory Warner, who also worked on the display. "They used glass plates and binder clips, because they were working really quickly all the time and they wanted something they could take apart and clean easily."*
        - *After synthesizing a gene for insulin, the scientists needed to assimilate it into a bacterium's DNA so that the organism would produce insulin on its own. They used a variety of enzymes to do so, including Eco R1, a chemical that cuts DNA in a precise location, based on the surrounding base pairs. Researchers extracted small DNA molecules called plasmids from the bacterium, severed them with these enzymes, then used other enzymes to stitch the synthetic insulin gene in place. The new hybrid plasmid could then be inserted into live bacteria.*
        - *Another subsequent innovation ushered in the age of biotechnology in earnest: polymerase chain reaction, or PCR, a chemical reaction developed in 1983 by biochemist Kary Mullis that allowed scientists to automatically multiply a DNA sample into greater quantities with significantly less manual work. The first prototype PCR machine, or thermal cycler, was based on researchers' knowledge of how enzymes like DNA polymerase (which synthesizes DNA from smaller building blocks) functioned at various temperatures. It relied on cycles of heating and cooling to rapidly generate large amounts of DNA from a small sample.*
        - [Bill] Private capital explicitly decided which biotech product Genentech would specifically attempt to produce after the scientists had developed a proof-of-concept showing they had improvised the equipment and developed the knowledge to make something: *Genentech's work began with a discovery made in the 1970s by a pair of Bay Area scientists, Herbert Boyer of UC San Francisco and Stanley Cohen of Stanford: Genes from multi-cellular organisms, including humans, could be*

implanted into bacteria and still function normally. Soon afterward, they teamed with venture capitalist Robert Swanson to form the company, with the hope of using genetic engineering to create a commercially viable product. ***Early on, they decided insulin was a logical choice. "It was convenient. It was an easy protein to handle, and it was obviously something that a lot of people needed,"*** *says Diane Wendt, a Smithsonian curator who worked on the display. [...] After the Genentech scientists successfully created bacteria with copies of the insulin gene, they confirmed that the microbes could produce human insulin in sufficient quantities in a fermentation tank like this one. Then the genetically modified bacteria were passed off to researchers at Eli Lilly, who began producing it in commercial quantities for sale. Voila: synthetic human insulin.*

- [Bill] Drilling down on this a bit further: https://www.labiotech.eu/in-depth/history-biotechnology-genentech/ (this 2020 blog post on Labiotech explains the role of private capital in the industry)
    - *However, to get the revolution going, the technology needed to reach the market. In January 1976, one of the scientists behind the study, Herbert Boyer, received a phone call. It was from a young venture capitalist called Robert Swanson, then a partner at the firm Kleiner & Perkins. Swanson was enthusiastic about the commercial potential of the recombinant bacteria and persuaded the reluctant Boyer to meet up for a few minutes. The meeting ended up lasting for hours, with Swanson convincing Boyer to found a company. The two made an initial agreement to invest $500 each (the equivalent of around [$2300] today). Boyer also came up with a name for the company: Genentech, derived from the words genetic engineering technology. [...] Genentech became the first biotech company to go public, raising $35M on its IPO (equivalent to around €100M today) in 1980. After many years of getting drugs to the market, the company was eventually acquired by the Swiss giant Roche in 2009.*
    - *Genentech's story is only one of many biotechs that sprang up in the early days of modern biotechnology. However, the company set many precedents for the biotech industry across the globe. With their tiny initial investments, the co-founders of Genentech set the trend for funding biotech ventures from venture capitalists. Biotechnology is a field in which both the costs and risks are high, making venture capital a common means for starting up a company. Genentech proved such an investment could be profitable when it was acquired by Roche. Nowadays, partnerships with or acquisitions by big pharma has become the goal of many small biotech companies.*
- https://americanhistory.si.edu/collections/object-groups/birth-of-biotech
- https://www.nature.com/articles/s41579-019-0293-3 From the abstract: *Antibiotic resistance is undoubtedly one of the greatest challenges to global health, and the emergence of resistance has outpaced the development of new antibiotics. However, investments by the pharmaceutical industry and biotechnology companies for research into and development of new antibiotics are diminishing. The public health implications of a drying antibiotic pipeline are recognized by policymakers, regulators and many companies.*
- Acknowledging one more thing:
    - https://www.hopkinsmedicine.org/henriettalacks/immortal-life-of-henrietta-lacks.html

- https://en.wikipedia.org/wiki/HeLa