A History of Biotechnology

Waseda University, SILS,
Science, Technology and Society (LE202)

What is biotechnology?

When we hear about biotechnology, we usually think about genetic engineering through the modern techniques of DNA splicing and transfer. However, the concept can be taken from a much broader perspective, in which we are simply referring to the use of living organisms, or their components in human manufacture.

Definition (Biotechnology)

Any use of biological organisms or processes in industrial, medical, agricultural and environmental engineering.

Under such a conception it becomes clear that biotechnology, like mechanical engineering, goes back to the first human civilizations, with the rise of animal husbandry and the use of fermentation processes in the production of food and drink.

Hence, the rise of microbiology in the 19th century lead to the development of *scientific* biotechnology.

Zymotechnology

Zymotechnolgy was the German term for the study of the processes of fermentation in yeast and bacteria in the production of foods and beverages such as bread, cheese, tofu, beer, wine, sake, nato, etc. In the 19th century, with the rise of big industries – particularly in Germany, Britain, the Netherlands, the US, and Japan – university-trained microbiologists began to isolate the microorganisms involved in these processes and to study them.

Using the techniques of scientific microbiology of the 19th and early 20th centuries, it became possible to isolate pure strands of the various yeasts and molds involved in these processes, so as to standardize the mass production of food and beverages. From the end of the 19th century, a number of industrial and governmental labs, and teaching institutions were established for training brewers and for maintaining pure stocks of the microorganisms required in brewing and wine making.

A scientific approach

The Pasture Institute set up a research brewery in 1876. The Berlin Technical University established the Institut für Gärungsgerwerbe (fermentation), in 1897; Birmingham University's British School of Malting and Brewing, 1899; Brewing Experiment Station was established in Tokyo, 1902. Many others followed.

A number of specialist journals were established such as Alfred Jørgensen's *Zymotechnisk Tidende* (Danish).

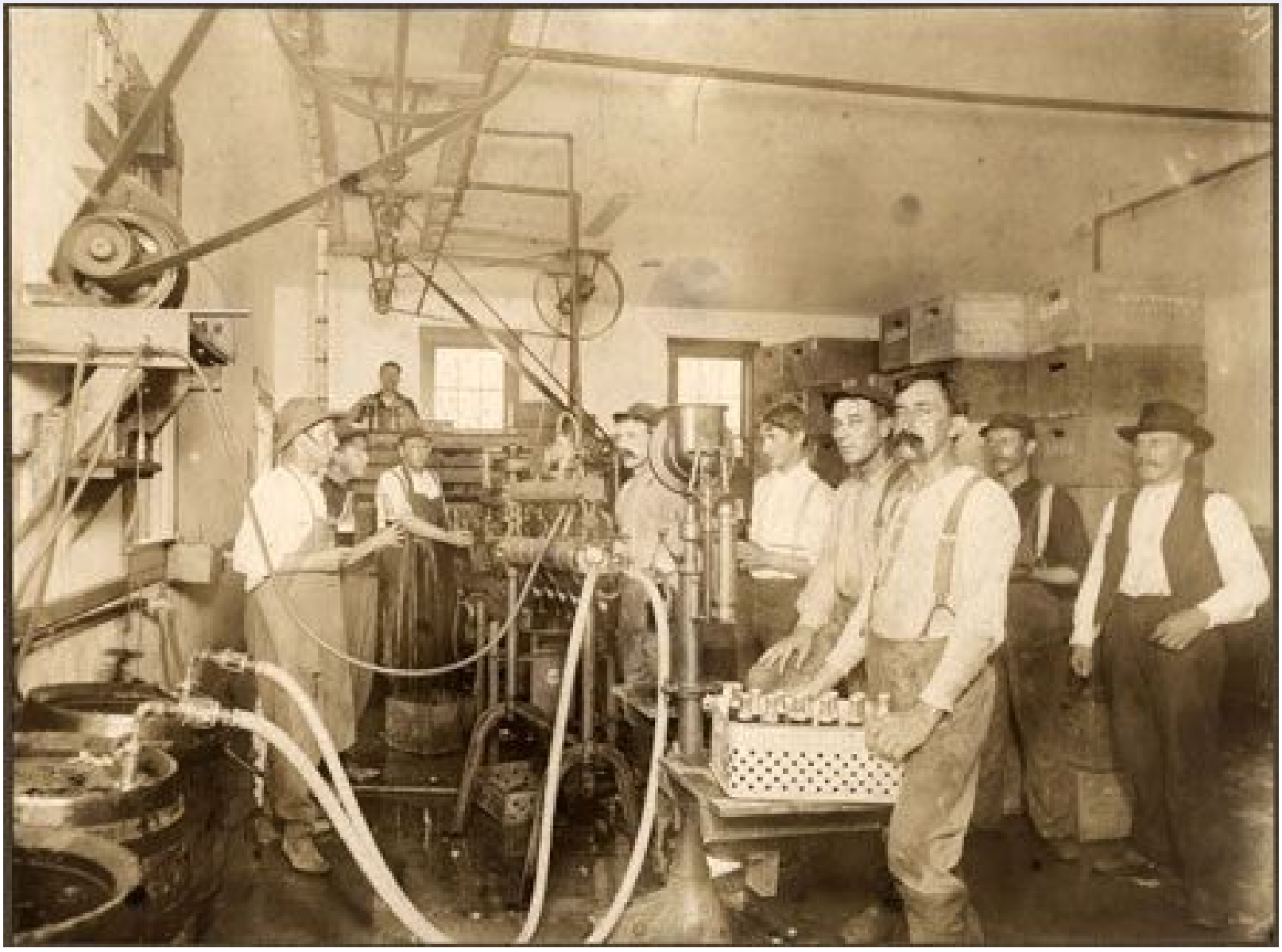
Jørgensen, *Practical Studies in Fermentation* (1896)

"Nowadays it must be clear to every zymotechnologist who has made himself familiar with the results of recent investigation, that wherever fermentation organisms are made use of, the aim must be the same, namely to give up the old traditional method which depended upon mere chance. In this entire field a new era has now commenced."

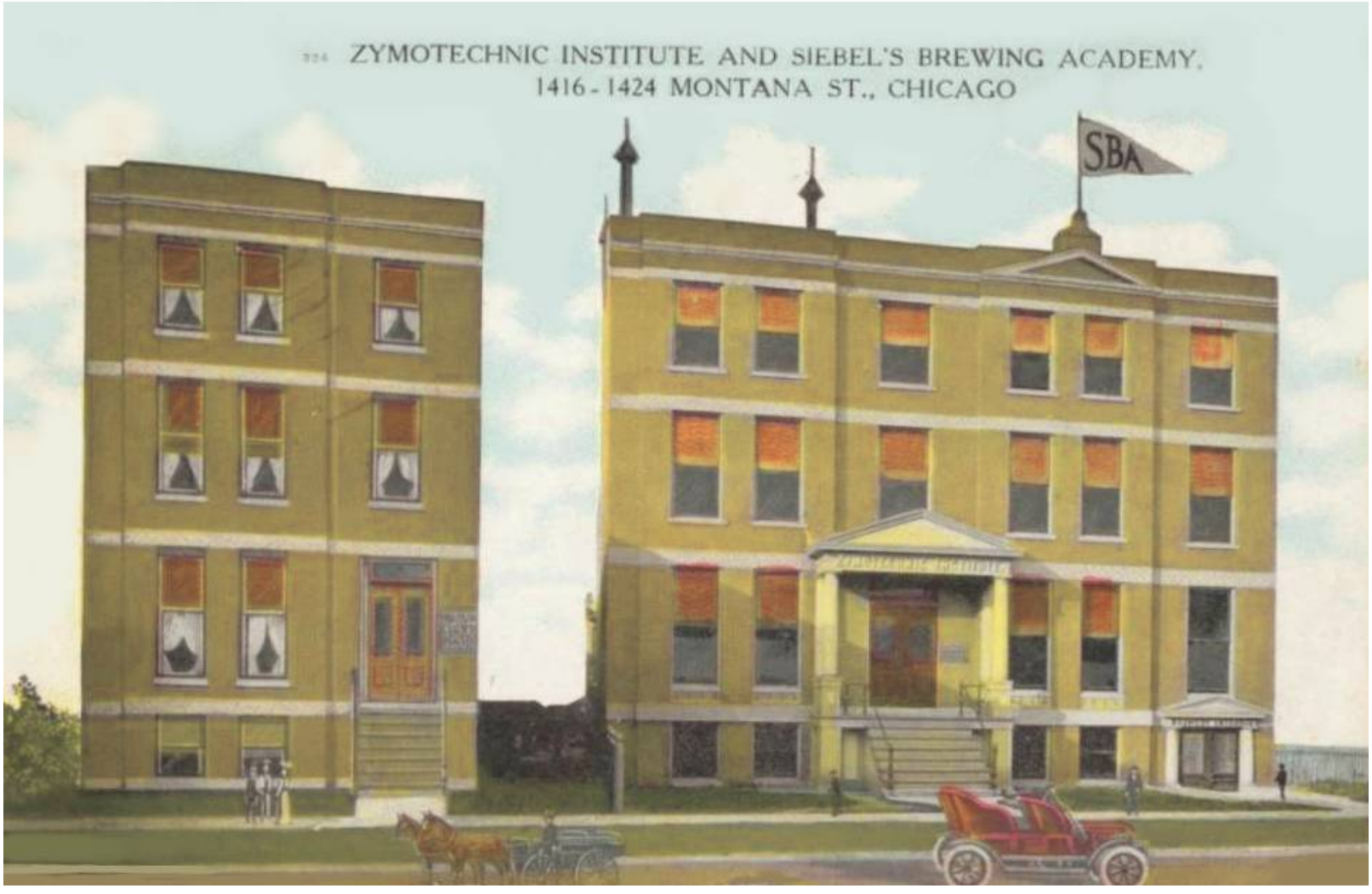
Institut für Gärungsgewerbe (Fermentation industry), Berlin

Osaka Brewing (Asahi), founded in 1889. We see the Japanese owners and workers, as well as some foreign advisors (zymotechnologists). We see Japanese text on the upper barrel, and the old German type (Fraktur) on the lower barrels.

In Japan, microorganisms were mostly studied within the field of Agricultural Chemistry (農芸化学).



Siebel's Brewing Academy, Chicago, around 1902



The Zymotechnic Institute, Chicago, around 1910

The Bureau of Bio-Technology

Emil Siebel (1884–1939), a son of the brewery owner, worked on using fermentation processes to develop a "temperance beer" during the US prohibition, and established a consultancy in 1917 that came to be called The Bureau of Bio-Technology – presumably as a nod to his proclaimed good relations with the Federal inspectors.

When prohibition came to an end in 1932, he went back to training and consulting with brewers and bakers. Although Emil Siebel's institute had no effect on academia, it seems to have influenced industry.

A microbiology consulting arm of Murphy in Leeds was also called the Bureau of Bio-Technology. The Leeds firm had a greater reach, because it published its findings on the significance of microbiological processes in brewing, backing, tanning, and various other industries.

The term “biotechnology”

The word “biotechnology” was coined by the agricultural engineer Károly Ereky (1878–1952), in Hungary in 1919, to describe general processes of converting raw materials into useful products, such as on industrial farms.

In the 19th century, Hungary had became a key agricultural supplier to the Austro-Hungarian Empire, with production centered on massive feudal estates. In the 1910s, Ereky set out a plan to revolutionize the agricultural production of the country; opposed to the old peasant methods, he proposed a *new industrial system*, which he called biotechnology. He established a massive industrial farm, raising and slaughtering 100,000 pigs a year – equal to 1/8 of the production of the entire country of Germany. Ereky described his system and philosophy in detail in a number of books – arguing that while past technology had been defined by the use of iron and stone, the future would be defined by the use of biology.

The Weizmann process for producing acetone, butane

In Britain, Chaim Weizmann (1874–1952) – a British zionist who later became the first President of Israel – developed bacterial fermentation processes for producing organic chemicals such as acetone, butane and cordite propellants from rice, corn and acorn fermentation.

- The importance of butane to synthetic rubber production was just becoming clear, and this was significant to the British, who did not want their rubber industry wiped out by a German success in synthesizing rubber.

During WWI, Weizmann was put in charge of British efforts to scale up to industrial levels of acetone production for explosives. These processes were then transferred to the US during the war. The so-called Weizmann process worked with a new organism, required a new degree of microbiological sophistication and required laboratory levels of sterilization in industrial production.

The sulfa drugs

In 1932, Bayer AG released Protosil, the first of a class of *synthetic* antibiotics known as the sulfonamides. This was a purely chemical drug group, that was developed out of the extensive work of the German textile industry in producing synthetic dyes from coal-tar.

Because the active ingredient was not patented, in the late 1930s, there was a "sulfa craze" and 10s of 1000s of tons of various drugs were produced. Although they were only effective for certain types of bacteria, they were the primary type of antibiotic used in medicine between the wars. Already by the late 30s and early 40s, it was clear that various bacteria were *evolving resistance* to the sulfonamides.

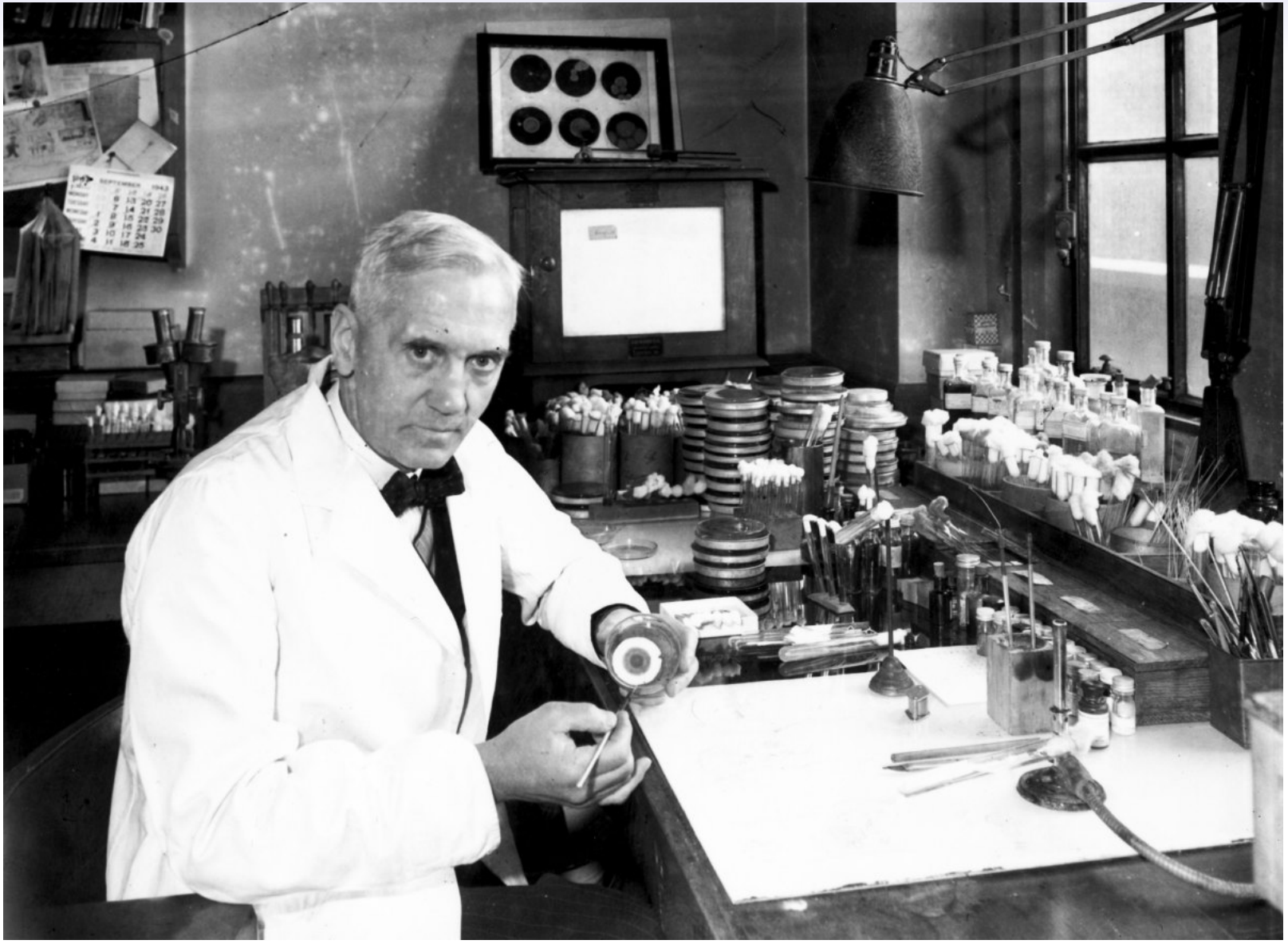
Since the production of the sulfa drugs was dominated by the German pharmaceutical industry, they continued to be the mostly widely used form of antibiotic in the Germanies until the 1960s.

Fleming's discovery

The story of the discovery of *penicillin* by Alexander Fleming (1881–1955) is one of the most famous tales of accidental discovery in the history of science. Fleming was a Scottish bacteriologist working at St. Mary's Hospital Medical School, London, who had studied various germ-killing compounds.

The story goes that he returned to the laboratory after a month's vacation to find a bunch of plates (petri dishes) that needed washing. He was going to throw them away, but instead kept one that had a small dark green mold surrounded by a sterilized ring.

He carried out a series of experiments on the mold showing that it killed some bacteria, but not others. He published his findings in the *British Journal of Experimental Pathology*, 1929. He had failed to separate the active compound, so he called a juice made from the mold *penicillin*.



Fleming was portrayed as a national hero in the wartime penicillin propaganda

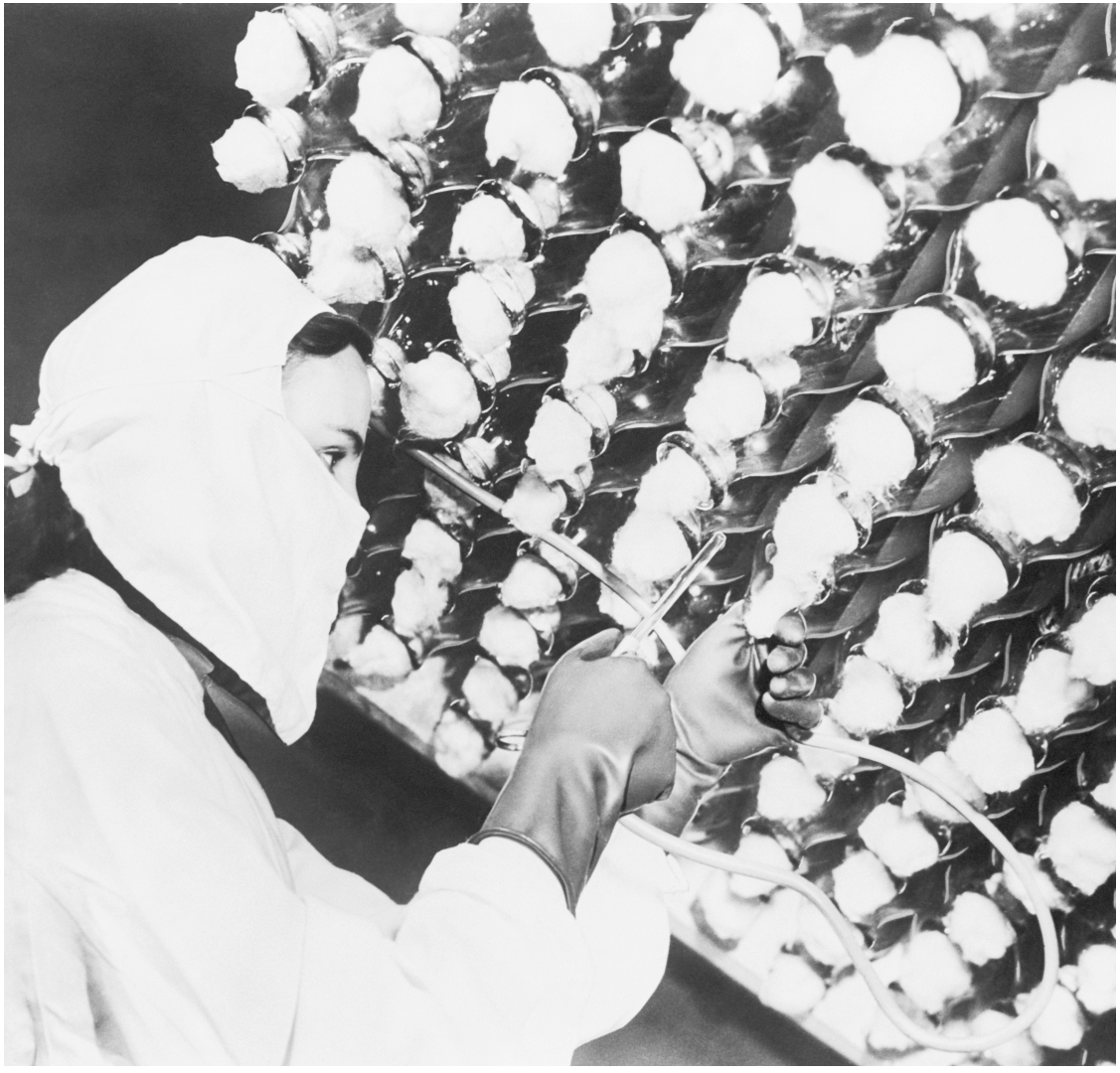
World War II: Penicillin production

- In 1940, a team of researchers at Oxford University found a way to purify penicillin and keep it stable. With the fall of France in 1940, the urgency to produce enough penicillin to try on human subjects increased. The British established a cottage industry, growing mold in pans and extracting penicillin in small batches.
- During the war production moved to the US. Pfizer, which had made fortunes using fermenting processes to produce citric acid in the 1920s, as well as number of other corporations, such as Merck, helped in the production of penicillin.
    - The process involved a complicated production process and new factories were opened to implement it: Pure strains of the mold were first grown in small bottles, then seed tanks, then deep fermentation tanks. The mold was then purified using a crystallization process. Using this new method, they were able to produce as much in a day as they had in the previous year.

Early British penicillin production

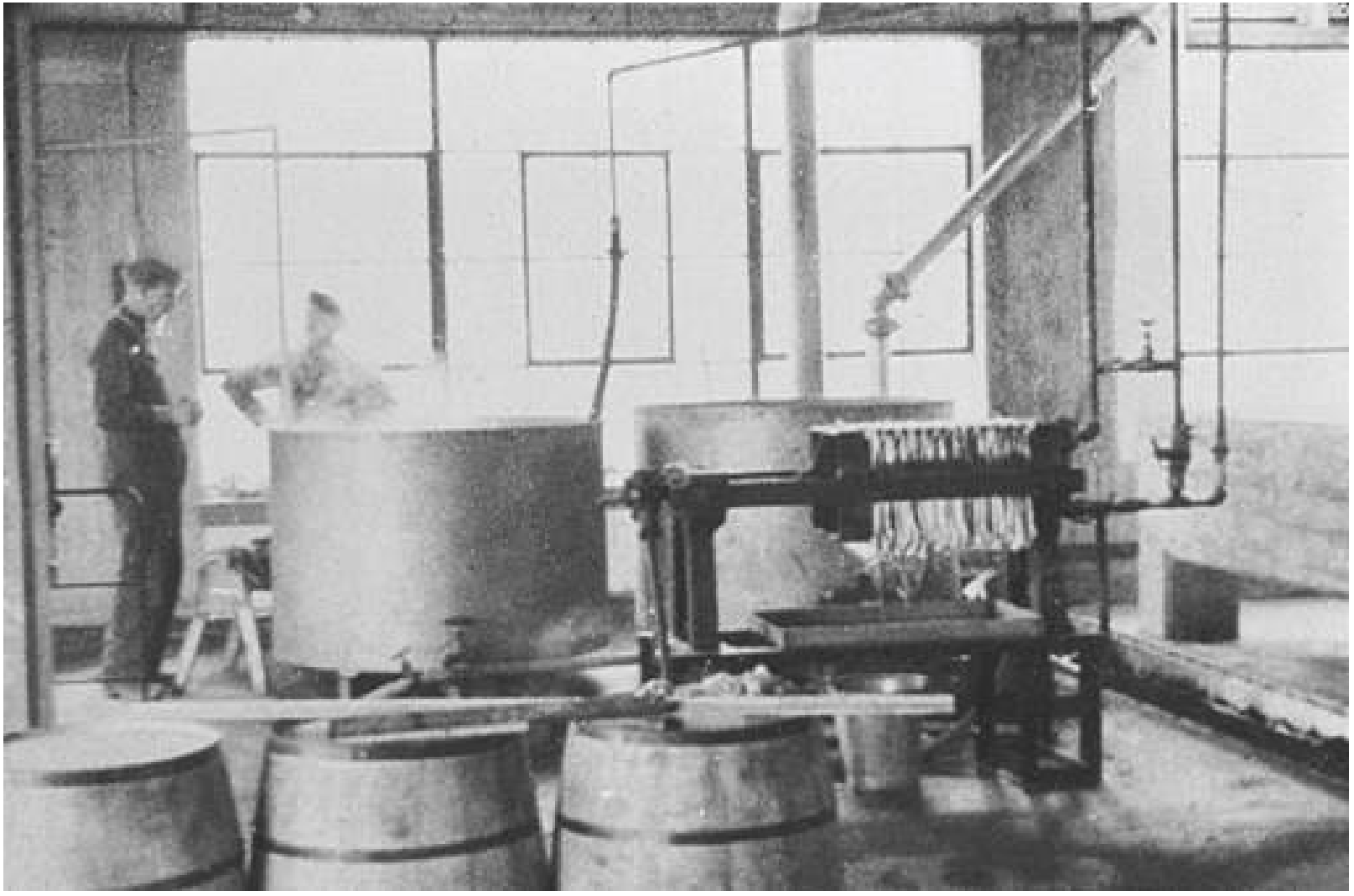
Ernst Chain's penicillin production setup

Penicillin production, 1944



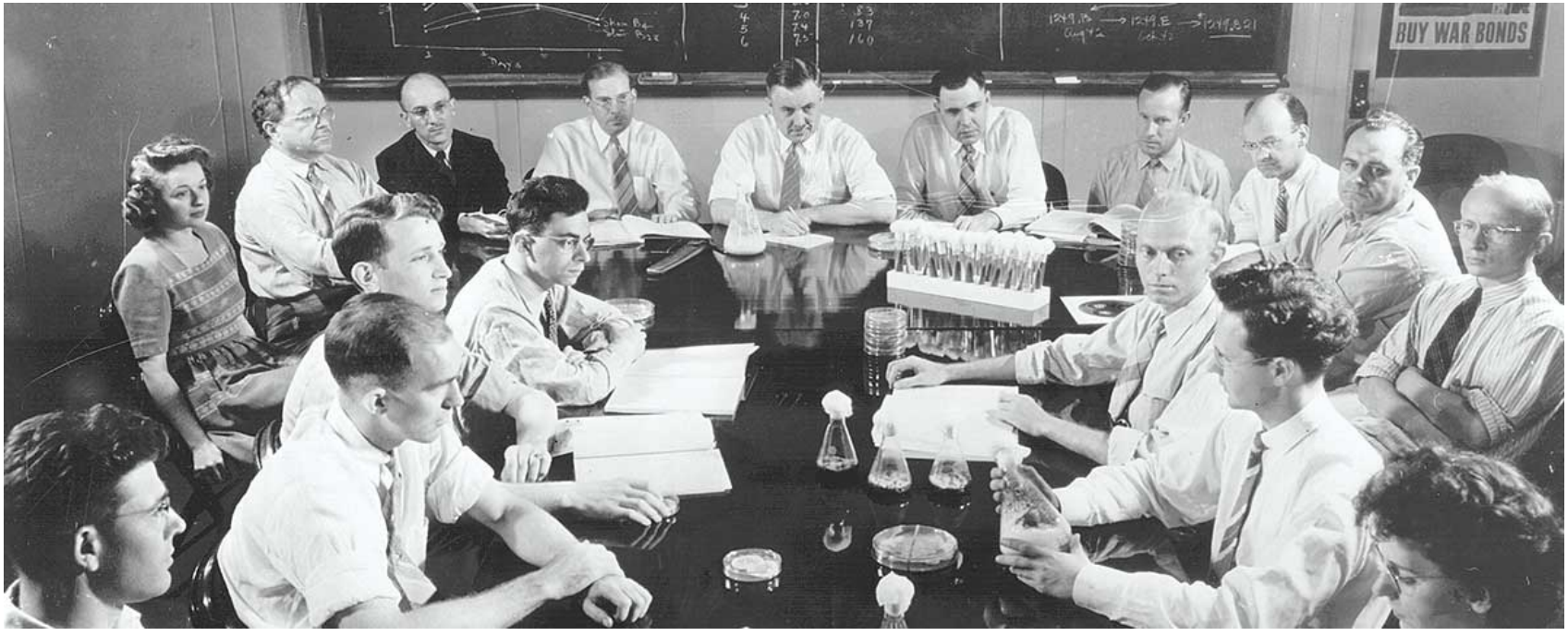
Growing the penicillin mold in individual flasks

Deep fermentation tanks



Early penicillin production in deep fermentation tanks

Teamwork



A penicillin meeting at the Northern Regional Research Laboratory, Peoria, Illinois, 1940s

Penicillin in WWII

The idea of penicillin played a key role in the wartime propaganda of the Allies. A major documentary movie was made, lionizing Fleming as a hero. Accounts of the use and history of the drug appeared in newspapers and magazines.

The new drug was tested on wounded soldiers returning from the invasion of Sicily in 1943. Shortly afterwards 700 US army physicians were trained in the use of penicillin. As production ramped up, there was soon enough for all casualties, both Allied and Axis – because the Allied doctors successfully argued that they were obliged to use the drug on the enemy wounded as well. Penicillin was also found to be highly effective at treating the venereal diseases that were becoming rampant in wartime.

By 1944, penicillin also became available for civilians, first in the US and then in other Allied countries.

A penicillin advertisement on the US streets

US wartime penicillin propaganda

Penicillin takes over the world

During the war there had been a number of groups who had started working on penicillin in small batches – in Germany, in occupied Czechoslovakia, Holland and France, the USSR, China, and Japan. Following the war, with the disruption of industry and agriculture, there were massive famines and disease epidemics, especially in the Axis countries. The only places where there was any penicillin *industry* was the US, Canada and to a lesser extent Britain. The distribution of penicillin became a major part of the Allied project of rebuilding under the United Nations Relief and Rehabilitations Agency, and later the World Heath Organization.

Through these agencies, American, Canadian and British penicillin engineers oversaw the production of penicillin plants all over the world. Other countries set up their own plants. In a matter of a few years, the techniques of penicillin production had been transferred from the US heartland all over the world.

Bacterial resistance

Throughout the 1940s and 50s, there was a growing recognition that bacteria were adapting to the antibiotics in their environment by being selected for resistance traits. Scientists and public health experts advised stricter control of antibiotics and reduced prescriptions, but medical professionals continued to prescribe indiscriminately, and in many jurisdictions antibiotics could, and still can, be acquired without prescription.

Kopronski, "The Future of Mankind" Conference, 1962

"To my great grandson, if he intends to become a healer: If a universal antibiotic is found, immediately organize societies to prevent its use. It should be dealt with as we should have treated, and did not treat, the atomic bomb. Use any feasible national and international deterrents to prevent it falling into the hands of stupid people who probably will still be in the majority in your time, as they were in mine."

Institutionalizing the engineering of nature

In 1937, MIT had established a department of Biological Engineering – defined as "the art of organizing and directing men and of controlling forces and materials of nature for the benefit of the human race."

After WWII, technoscientists began to institutionalize biotechnology in various ways – to establish departments, institutes and ministries. During the war, a number of countries had used biotechnological means to supplement their shortages – for example, the Germans and Japanese produced lab grown proteins for feeding their livestock. These labs were now institutionalized.

The first department of Biotechnology was founded at UCLA in 1944, and, in the 1950s-60s, became widely respected for its work on man-machine interfaces. In Japan, biotechnology was studied in departments of Agricultural Chemistry. The Swedish Academy opened a section of *biotecnik* in 1942.

The promise of a green technology

In the early Cold War period, biotechnology was considered an alternative to the new technologies developed by the "military-industrial complex," which were increasingly seen as "earth destroying." It was hoped that biotech might solve major social problems, such as energy and food shortages.

- Imitation rhizobia: There were projects to try to develop bacterial fertilizers that could convert nitrogen to ammonia like the rhizobia bacteria does in beans.
- Biogas and gasohol: In countries like China and India, there were projects to convert biomass into fuel. In 1974, Brazil began a massive project to convert sugar cane to gas.
- Single-cell protein: During WWII, the Germans grew single-cell (fungal) protein for animal fodder. In 1968, the Japanese produced 110 tones of single-cell protein bacteria.

Quorn, a food product made with mycoprotein

Biotechnology in postwar Japan

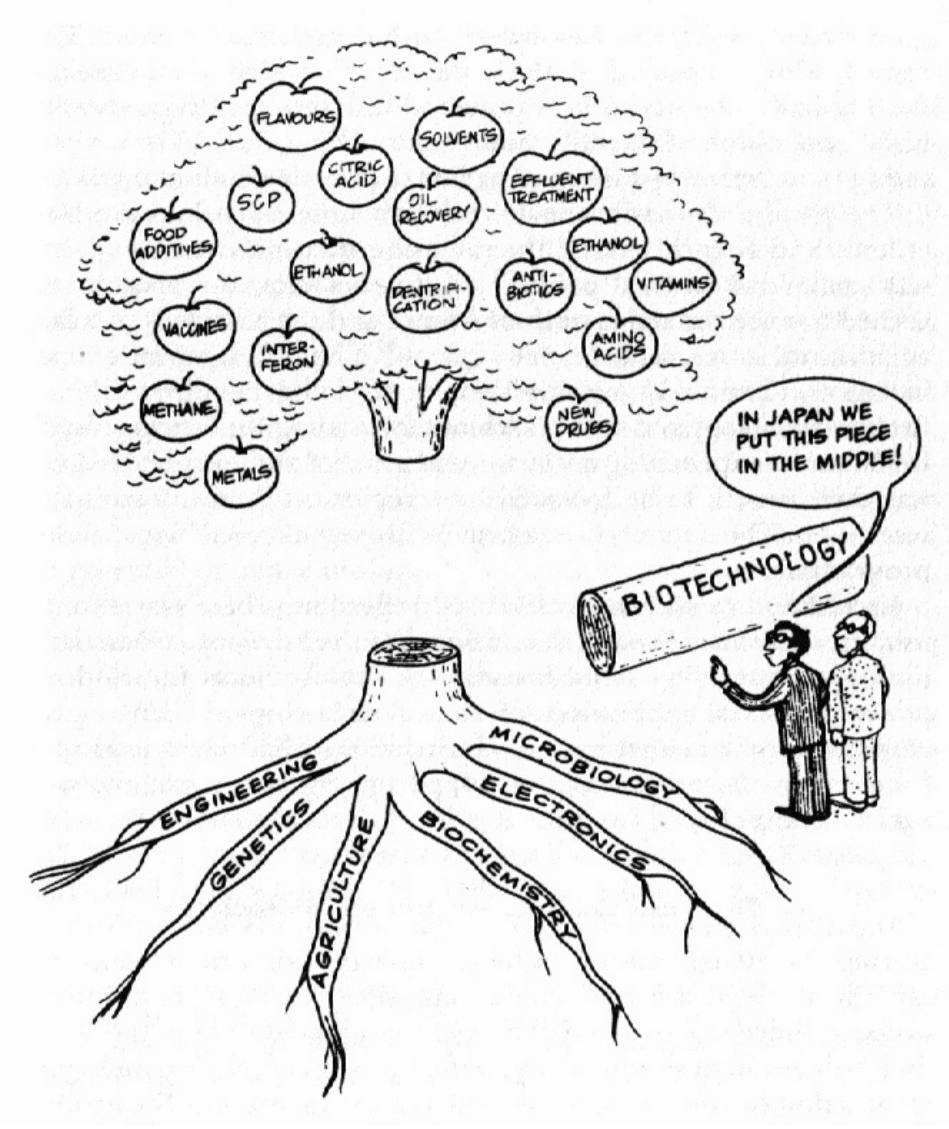
Japan's history of the use of fermentation processes (発酵, 醗酵) gave Japanese technoscientists a broad conception of biotechnology. Japan was the first country after North America and Britain to achieve self-sufficient penicillin production. In Japan's high-growth period, the country became a world leader in biotech. Corporate labs took the lead in research and development.

Antibiotics: industrial fermentation methods, research into antibiotic resistance, development of new mold-based drugs like statins and avermectin, etc.

MSG and Flavorings: biotechnical production of MSG, technological transfer out of Japan, opening the global marked for food flavorings, etc.

Metabolic Engineering: research into the metabolic pathways of chemical production in microorganisms, production of primary metabolites like amino acids and nucleotides, production of chemicals for industrial production, etc.

Cartoon from the *New Scientist*, 1979



Genetic engineering

The mature stage of biotechnology began with the advent of genetic engineering, using the new techniques of *molecular biology*. Following the discovery of the molecular structure of DNA, two key events in this process were the development of the recombinant DNA (rDNA) techniques and polymerase chain reaction (PCR) techniques. These techniques could be used to transfer genes from one organism to another and to copy trace amounts of DNA to produce a sizable sample.

These developments brought biotechnology into the public eye, and along with the first transplant of a human heart in 1967, brought home for people the realization that human biological nature might be *flexible*. Responses to the ever increasing technological accomplishments were a mixture of awe and suspicion. "Cloning" became a topic for science fiction in the 1970s. By the 80s, biotechnology was a nascent industry, with trade organizations and publications.

Recombinant DNA (rDNA)

1973, Stanley Cohen (1922–) and Herbert Boyer (1936–) developed a technique for splicing together strands of DNA from more than one organism called *recombinant DNA* (rDNA). Boyer had been studying an enzyme that cuts DNA, so that one severed piece latches onto another piece possessing a complementary cut. Meanwhile, Cohen had been studying *plasmid* DNA in *E. coli* and showed that they replicate independently of the bacterium's (usually circular) chromosomal DNA.

In their joint project, they showed that a gene that gave *E. coli* resistance to a certain antibiotic, tetracycline, could be spliced into plasmids and then transferred into non-resistant *E. coli* bacteria. The plasmids then reproduced in the new bacteria, rendering them resistant as well.

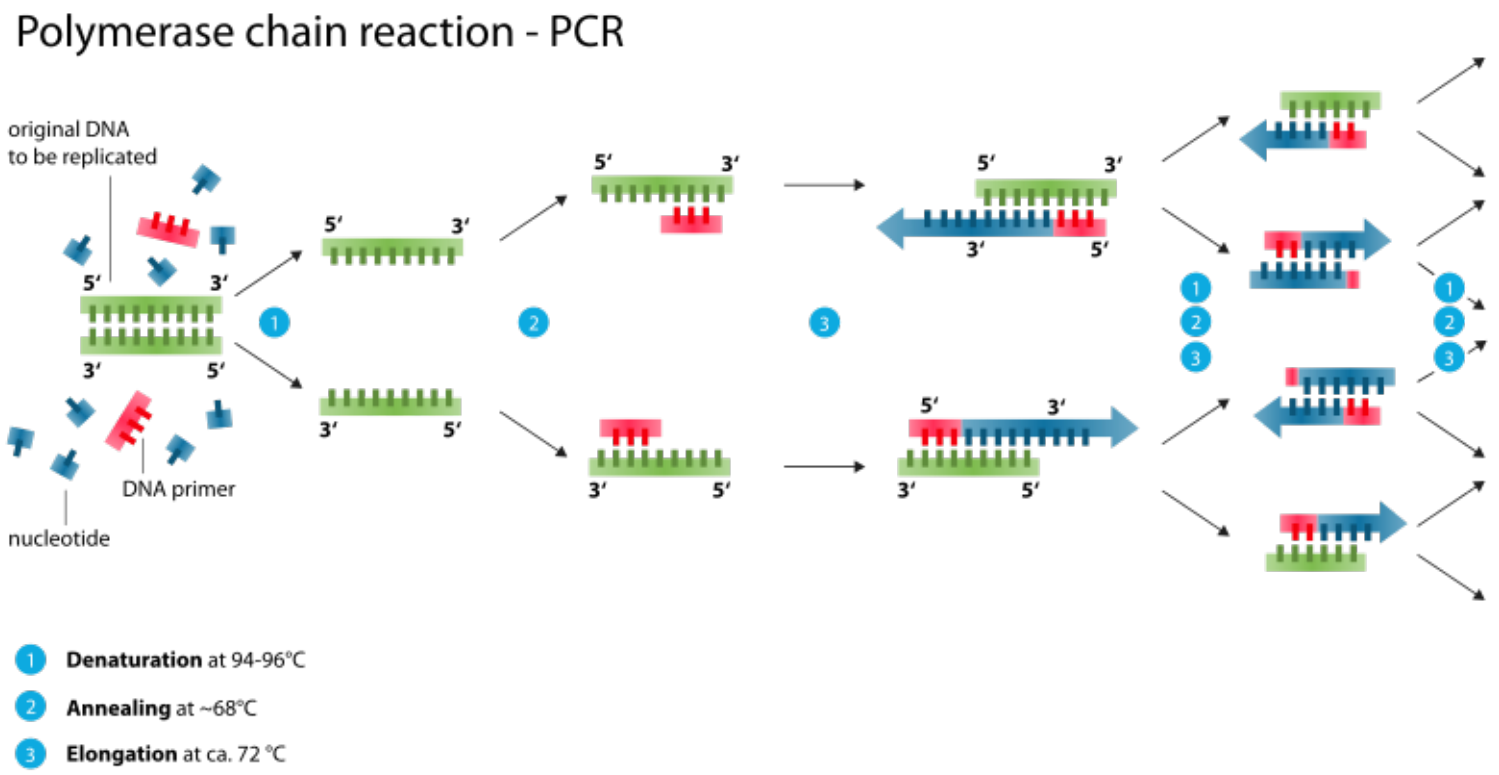
They then went on to show that genes could be *spliced into an organism of a different species* using similar techniques.

Polymerase chain reaction (PCR)

In 1983, while working at Cetus Corporation in Emeryville, California, Kary Mullis (1944–) developed a technique called polymerase chain reaction (PCR), which allows a piece of DNA to be replicated over and over again. He claimed that he had the idea in a sort of eureka moment while driving along the California coast, and in retrospect it does seem like the sort of technique that anyone working in the field could have discovered.

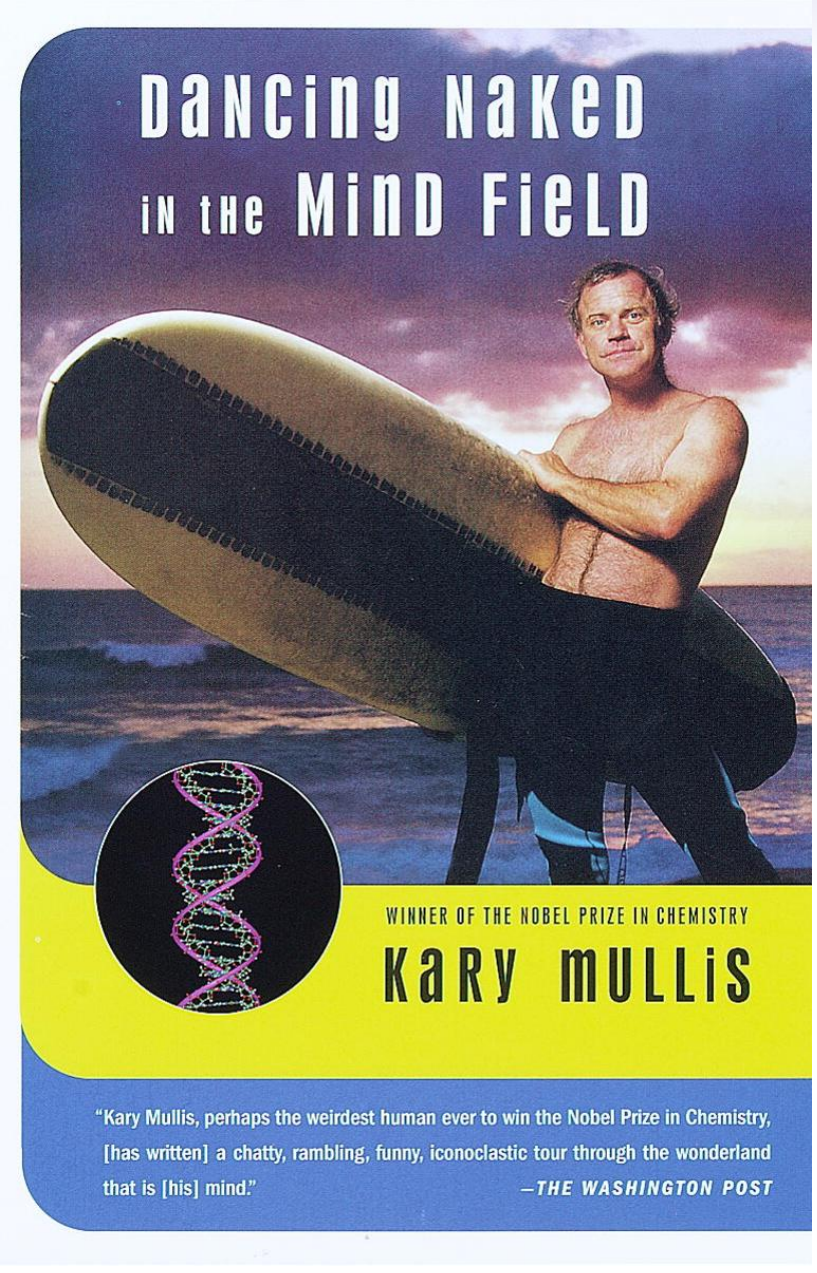
The idea was to heat up the solution of DNA to cause the strands to separate – to denature – and then cool it and mix it with primers – pieces of DNA that begin in the same way as the sequence one is interested in copying – and then warm it a bit so that new strands form following the primers. This process is then repeated in cycles, doubling the section of DNA to be replicated with each cycle.

Schematic of polymerase chain reaction



The basic steps of PCR

Kary Mullis famously went surfing on the day that his Nobel Prize was announced. When he finally came in from the water, reporters were lined up on the beach to interview him and take his picture.



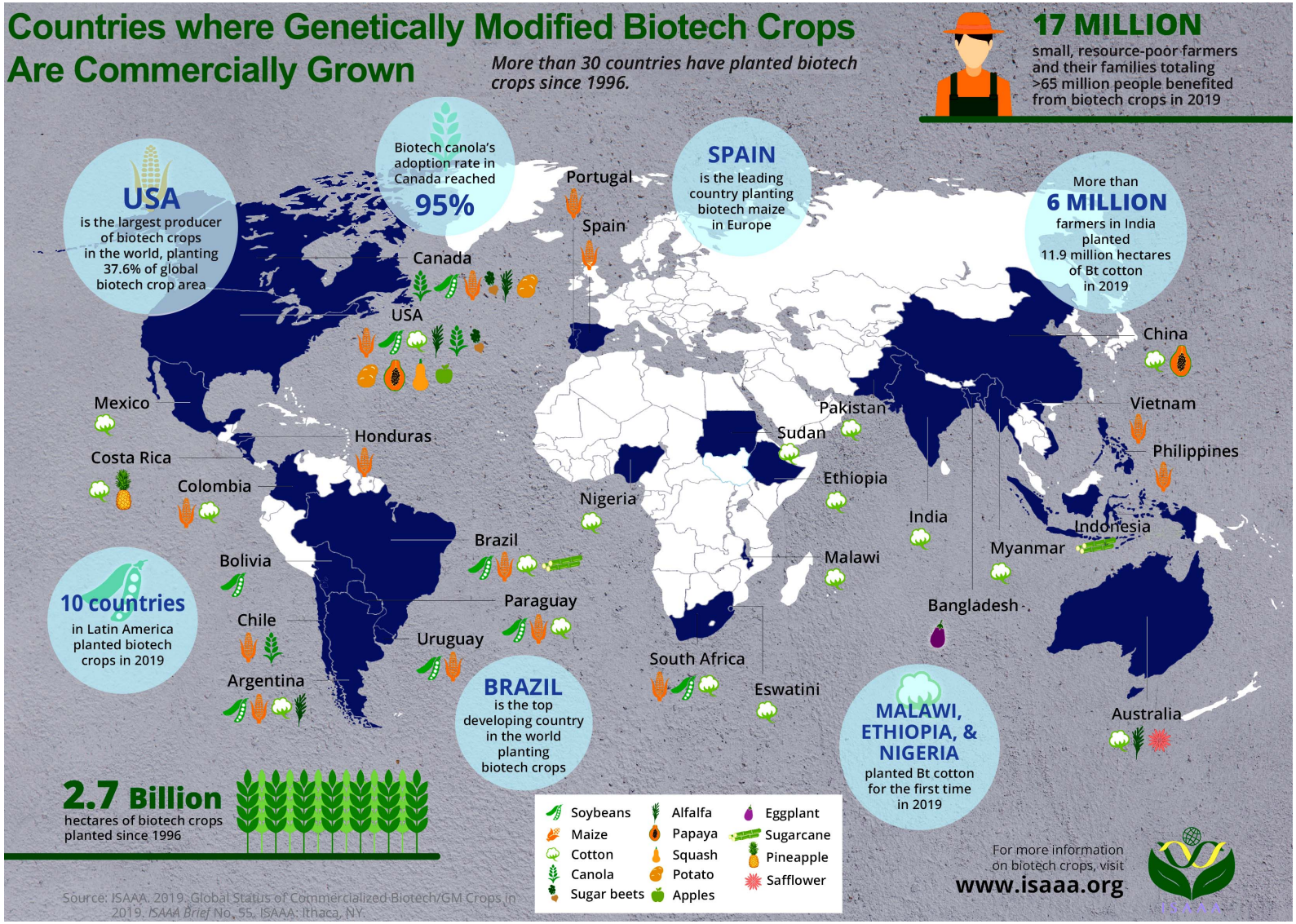
Corporate interests and control

- The debates about biotechnology and genetically modified products, however, have been strongly influenced by corporations that profit from this research.
- The framework of the debate has largely been set by the ideologies of *scientism* and *technological progressivism*, with relatively little attention paid to social, political and economic factors.
- The patenting of genetic products have given the corporate holders of these patents considerable strength, especially in the agricultural sector.
- Japan, Europe and Africa have been much more successful than the U.S. at implementing a more complete dialog on these issues that is not completely dominated by corporate interest.

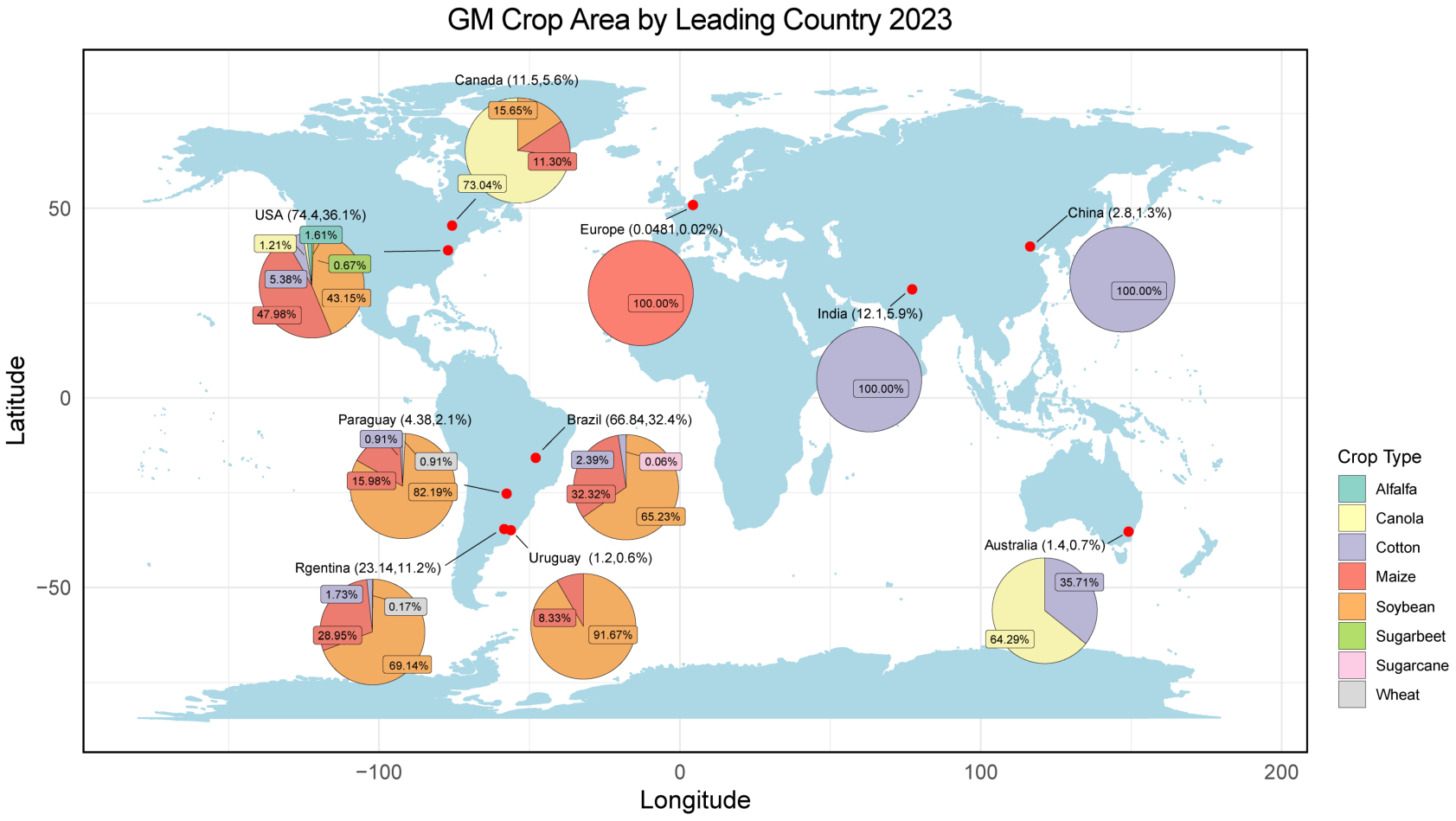
Genetically modified organisms (GMO) and foods

- Using rDNA techniques in GMOs can produce various effects:
  - Resistance to herbicides, resistance to pests and diseases, higher nutrient loads, etc.
- In 1993, the US FDA declared that GM food was safe. The rest of the world also appears to be moving towards this position.
  - The production of genetically modified crops is a sector that has generally been expanding in the last 30 years.
- The use of genetically modified crops is protected by license (similar to software), which makes these crops prohibitively expensive for many farmers.
  - For example, Monsanto charged Argentinian farmers license fees when they tried to sell their GM crops in Europe.
- One major concern with GM crops is "genetic drift," in which GM crops begin to "contaminate" the nearby crops or the wild populations.

GM crop production worldwide, 2019

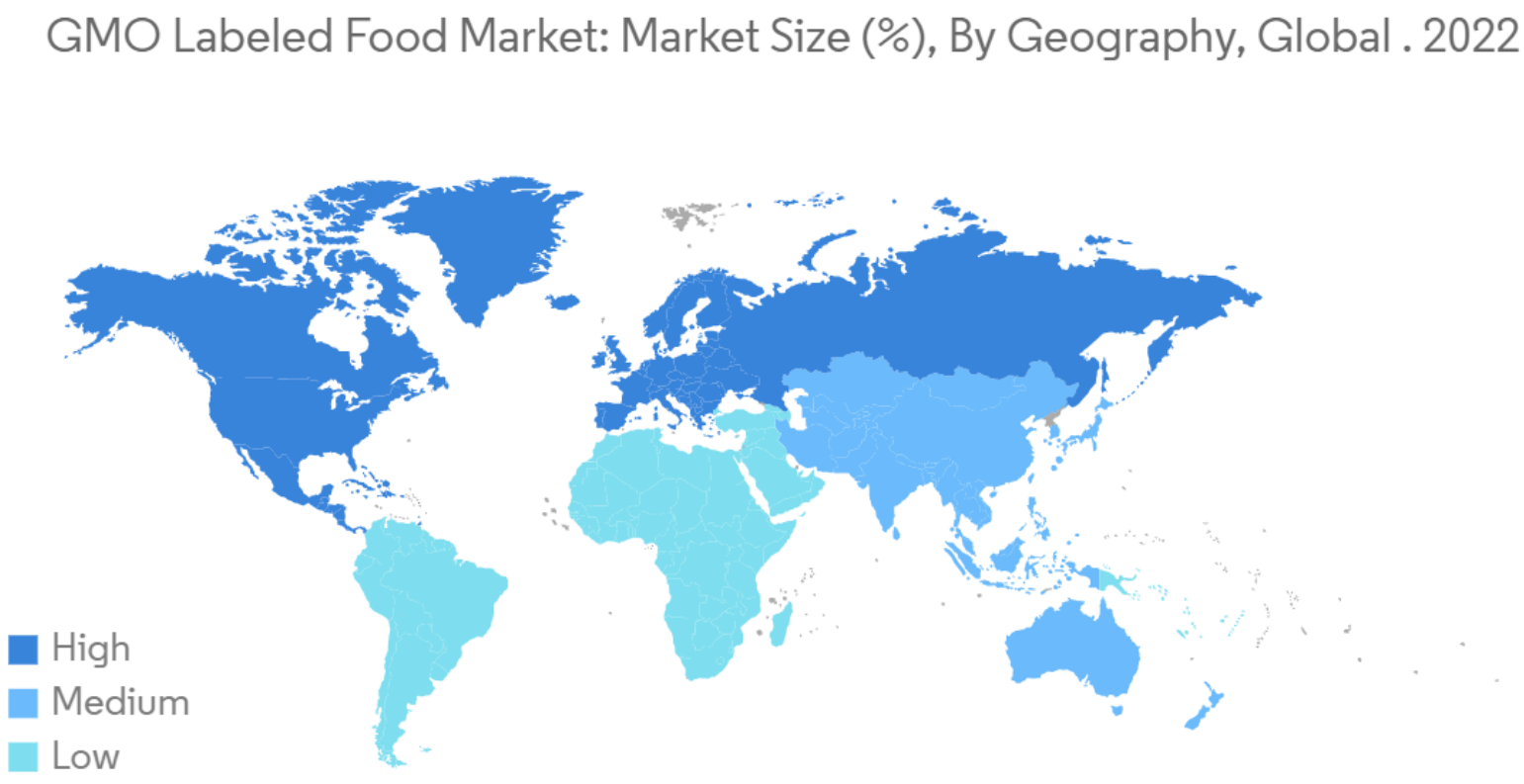


GM crop types, 2023



Countries that label GM foods, 2016

Countries that label GM foods, 2022



CRISPR Gene-Editing

Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR) were discovered in 1987 by researchers in Japan and elsewhere, to be produced in prokaryotic DNA from viruses, where they subsequently provide some immunity to such viruses. In 2002, Jansen and his team coined the term CRISPR, and discovered a group of genes around them known as the Cas genes.

Since 2012, Doudna, Charpentier, and others reengineered the CRISPR/Cas system to do targeted editing of the genome in human cells, and other eukaryotes. CRISPR is currently the state of the art in bioengineering, allowing us to edit the genome in the embryo, but also to interfere or alter the functioning or expression of genes, without permanently altering the genome itself.

China is taking the lead in using CRISPR to edit human genes.

- In 2018, He Jiankui, Shenzhen, China, used CRISPR to add a gene related to HIV resistance to two human babies.

CRISPR Successes and Concerns

The CRISPR biotechnology has been used to produce mosquitoes that are immune to the parasite *Plasmodium falciparum*, which is the root cause of malaria. These malaria resistant mosquitoes passed on their resistance to 99% of their offspring.

Researchers are using CRISPR to modify the genes of pigs, so that the pig's organs might be used to replace failing organs in humans. There are still some problems to be worked out, but researchers hope that pigs might produce a large supply of backup organs.

There are also, however, concerns that CRISPR will be used to modify human sex cells in ways that will allow parents, and others, to select for certain traits and screen against others. This raises, once again, the old questions about the extent to which humans should intervene in the genetic selection of other humans, their children or otherwise.

Big Pharma

- The majority of medications are brought to market by a small number of large multinational pharmaceutical companies, which have profit as their primary, or only, motive.
- They receive public money for much of the research that they use, but they lobby to receive patent protections on the drugs they make, and they focus on profitable drugs and markets.
- They engage in price gouging, and some companies buy the rights to certain drugs and then raise the prices. (Ex., Martin Shkeli, in the US +5000%.)
- The burden of proof to show effectiveness and safety is often quite low (they do not need to show the results of all trials), and many companies have had drugs taken off the market, or been fined for breeching protocol.
- Big Pharma is very powerful internationally, and has been able to establish a "friendly" regulatory environment.

Final Remarks

- We have looked at the historical development of the concept of using biological processes in engineering and manufacture.
- We have seen the rise of the pharmaceutical and agricultural use of biotechnology, based on genetic engineering.
- We have seen that biotechnology and genetic engineering has has come to be seen as a major key to economic development.
- We have seen that are a number of dangers and concerns with these new technologies.
- In the story of biotechnology, we see the boundary between science and technology, knowledge and power, becoming blurred.
- We see that in this field the Mertonian norms, which had been seen as a standard of scientific practice, are consistently and intentionally breached.
    - The recent SCOTUS decision is contrary to this general trend.