Biotechnology

Zymotechnology, penicillin,

and the rise of genetic engineering

Waseda University, SILS,
History of Modern Earth and Life Sciences

Putting organisms to work

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.

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 and the US – 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

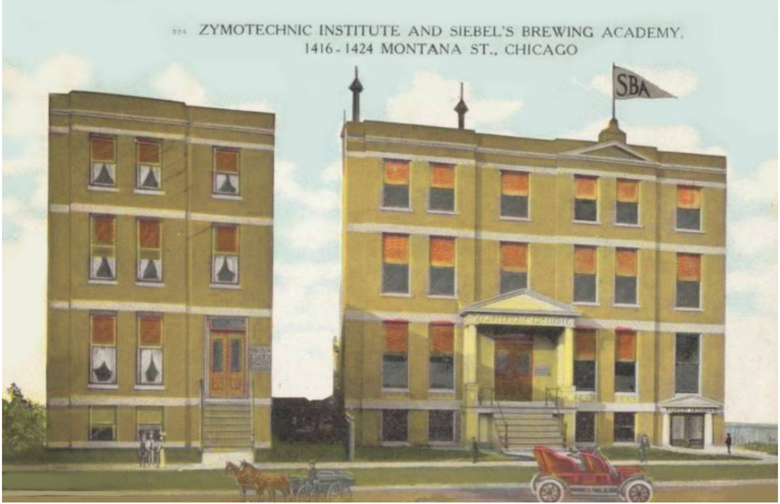
The Pasture Institute set up a research brewery in 1876. The Berlin Technical University established the Institut für Gärungsgerwerbe (fermentation), in 1897. Birmingham University's British School of Malting and Brewing opened in 1899. Many others followed.

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

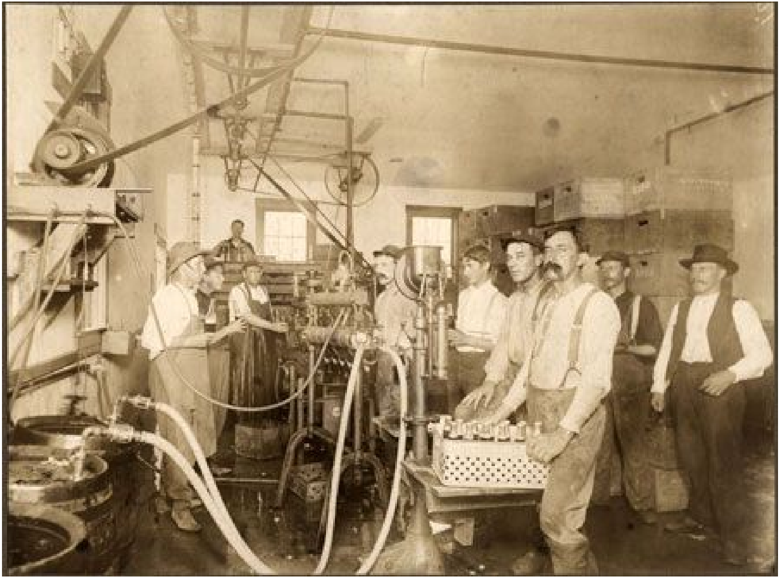
Jørgensen, *Practical Studies in Fermentation* (1896)

"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, Berlin



The Zymotechnic Institute, Chicago, around 1910



Siebel's Brewing Academy, Chicago, around 1902

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 it.

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 Weizmann process worked with a new organism, required a new degree of microbiological sophistication and required laboratory standards of sterility in industrial production.

Philosophies of biotechnology

During the interwar period, philosophers, sociologists and public intellectuals began to reflect on the growing link between biology and technology. They put forward the idea that biotechnology could be used to change human nature, and by changing human nature to change society.

The Austrian Raoul Francé (1874–1943), for example, claimed that we could regard life as a series of technical problems, for which living organisms acted as optimal solutions.

In Britain, biotechnology was conceived of as a possible solution to the damages of the industrial revolution. Patrick Geddes (1854–1932), the Scottish biologist, divided the history of technology into three stages: *paleotechnic* (1st industrial revolution), *neotechnic* (2nd industrial revolution) and *biotechnic* (future industrial revolution).

Raoul Francé's vision of a harmonious engineering

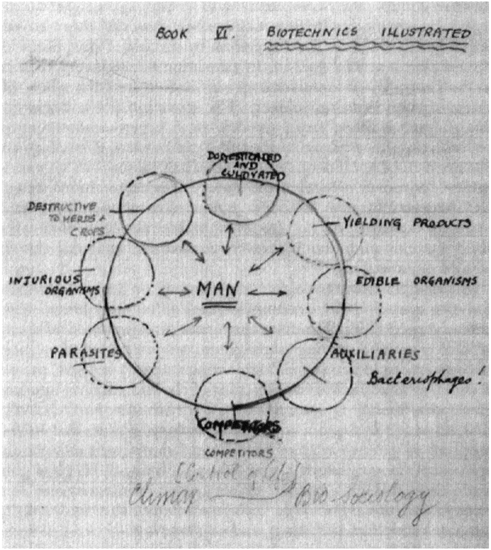
Francé, *Plants as Inventors*, (1920)

"It was my thesis that we can conquer not only by the destruction of disturbing influences, but by compensation in harmony with the world. Only compensation and harmony can be the optimal solutions; for that end the wheels of the world turn.

To attain its aim, life: to overcome obstacles, the organism — plant, animal, man, or unicellular body — shifts and changes. It swims, flies, defends itself and invents a thousand new forms and apparatuses.

If you follow my thought, you will see where I am leading, what is the deepest meaning of the biotechnical tokens. It portends a deliverance from many obstacles, a redemption, a straining for the solution of many problems in harmony with the forces of the world."

Patric Gedde's construction of biotechnics, notes



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 10 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.

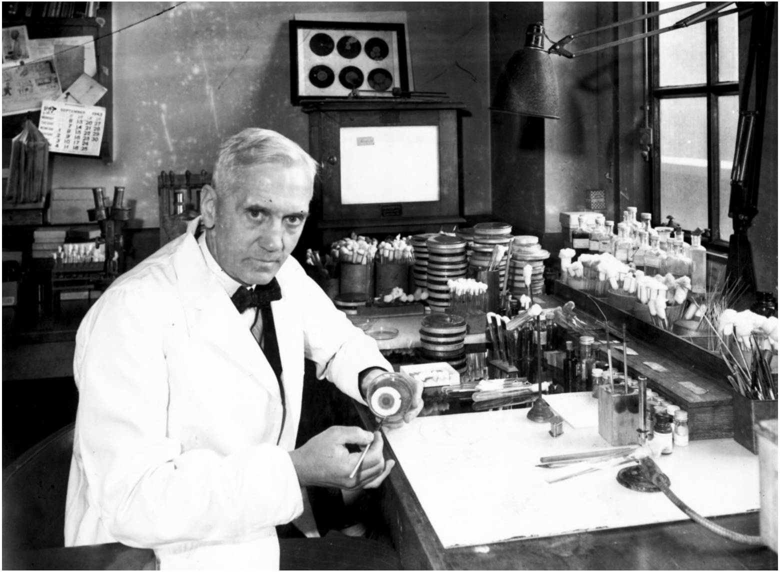
Since the production of the sulfa drugs was dominated by the German pharmaceutical industry, they continued to be the mostly widely used form of antibiotic in Germany until the 1960s.

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 some germ killing compounds.

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

He carried out a series of experiments on the mold showing that it killed some bacteria, but not others. He published in 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 made into a national hero as part of the penicillin propaganda

British developments in penicillin

In the late 1930s, a team lead by the Australian Howard Florey (1898–1968) at Oxford, including the Jewish-German emigre biochemist Ernst Chain (1906–1979) and Norman Heatley (1911–2004), succeeded in isolating a fairly pure form of penicillin (later found to be only about 1%). The resulting powder was injected into two mice, which did not have an immune reaction.

With the fall of France in 1940, the urgency to produce enough penicillin to try on human subjects increased. After six months, using new extraction equipment, the Oxford team injected penicillin into a policeman who had become badly infected from a simple rose prick. He seemed to recover, but eventually died. Of five more infected patients, four recovered and one died. The British established a cottage industry, growing mold in pans and extracting penicillin in small batches.

Early British penicillin production

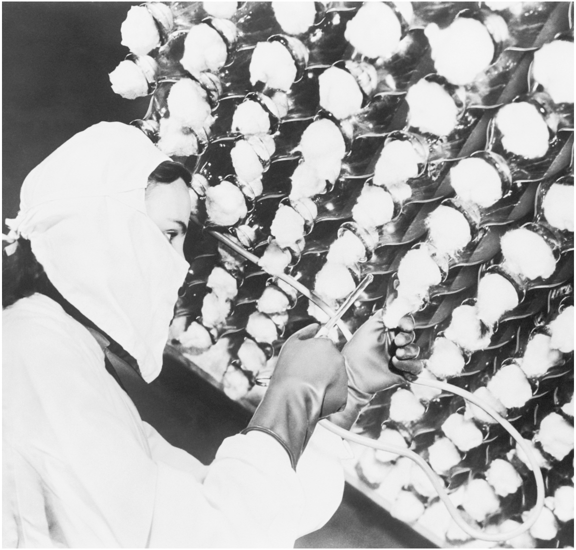
E. Chain's penicillin production setup

The US takes over penicillin production: Big science

The Oxford group had been funded by the Rockefeller Foundation, under the direction of Warren Weaver (1894–1978). Weaver funded Florey and Heatley to travel to the US to consult on the establishment of a new industry. Eventually, they went to the Northern Regional Research Laboratory in Peoria, Illinois.

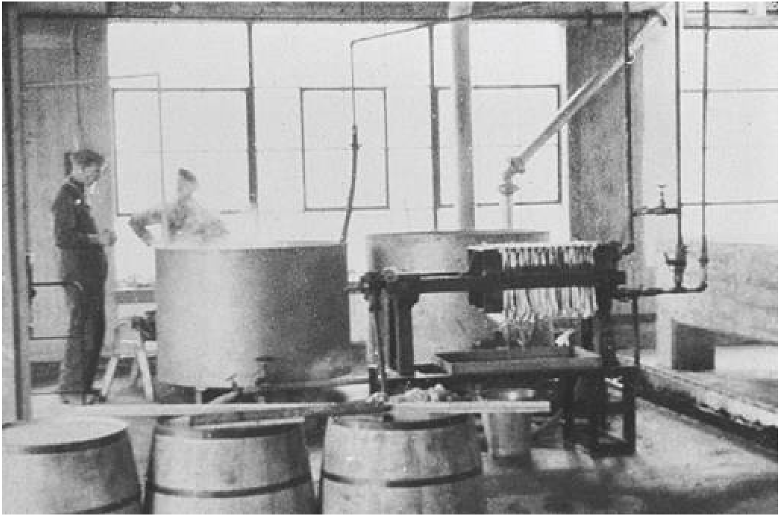
The Peoria group had expertise in deep fermenters that could be used to produce the mold on a massive scale. They changed the organism and the nutrients and ramped up production to industrial levels. In the US context, penicillin production began to involve government agencies, the military, big business and wartime propaganda. Labs all over the country took on scientific aspects of the project and production was handled by small chemical firms like Merck and Pfizer, and the whole project was organized from the top down by scientific advisory boards in close communication with the military.

Penicillin production, 1944



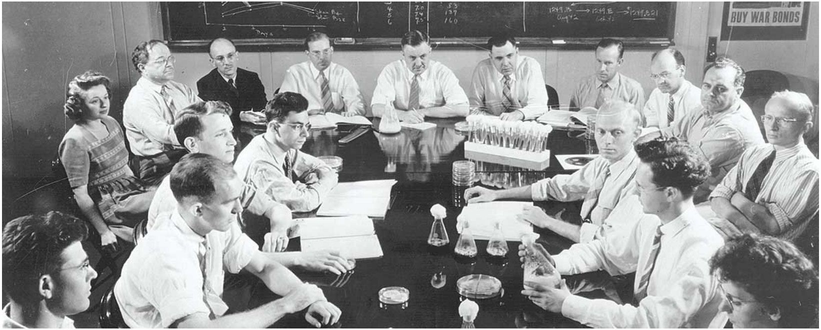
Growing the penicillin mold in individual flasks

Deep fermentation tanks



Early penicillin production in deep fermentation tanks

Teamwork



A penicillin meeting at the Northern Regional Research Laboratory, 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.

Florey tested the new drug on wounded soldiers returning from the invasion of Sicily in 1943. Shortly afterwards he trained 700 army physicians 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.


THRASH THE AXIS
BUY BONDS
PENICILLIN
CURES
GONORRHEA
IN 4 HOURS
SEE YOUR DOCTOR TODAY


Thanks to PENICILLIN
...He Will Come Home!


A Prayer Is Answered
Shell Research opens the way to great increases in production of the miracle drug PENICILLIN
PENICILLIN has been called the "greatest single drug ever known to mankind." The need for the drug—in human terms of tens of thousands wounded, hundreds of thousands of civilians sick or injured—became a prayer . . .
Could production of penicillin catch up with the need? One formidable stumbling block: penicillin, as produced in a "broth" by the parent mold, was unstable—quickly became inactive in handling—and was extremely difficult to "recover" from the broth. Despite efforts of many scientists, up to half of the drug was being lost.
This was primarily an extraction problem—and a tough one. Shell's special ability in this field has long been recognized; as a result, the penicillin recovery problem was brought to Shell Research . . .
Although it was off the beaten track of petroleum research, it had a familiar sound. Here the need was to "recover" something being lost. For many years, Shell scientists have been identifying, segregating, and recovering "lost" elements from the complex molecular structure of petroleum—such as the materials necessary to make 100 octane gasoline, or toluene for TNT. They went to work on samples of penicillin broth.
RESULT: After intensive research Shell developed a new recovery process by means of which production of penicillin could be substantially increased—in some plants even doubled!
Since proved in full-scale production, today 5 producers of penicillin have in operation—or under construction—recovery plants of Shell design.
Shell is grateful for the opportunity to bring this research discovery to the great cause of healing. No affiliated Shell company produces or sells penicillin, although Shell experts supervise the design and construction of new plants using the Shell process, and oversee their initial operation.
Look to this research leadership for greater fuels and lubricants. In their own field of petroleum research, Shell scientists have made striking contributions to the war. These will "carry over" to your post-war motoring—in finer fuels and lubricants for your car—ready when the word comes.
For distinguished service—Shell's Martinez and Wood River Refineries have been awarded the Army-Navy "E"
ARMY E NAVY
SHELL
Horizons widen through Shell Research
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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, in the USSR, China and Japan. Following the war, with the disruption of industry and agriculture, there were massive famines and disease epidemics 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 environments 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 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."

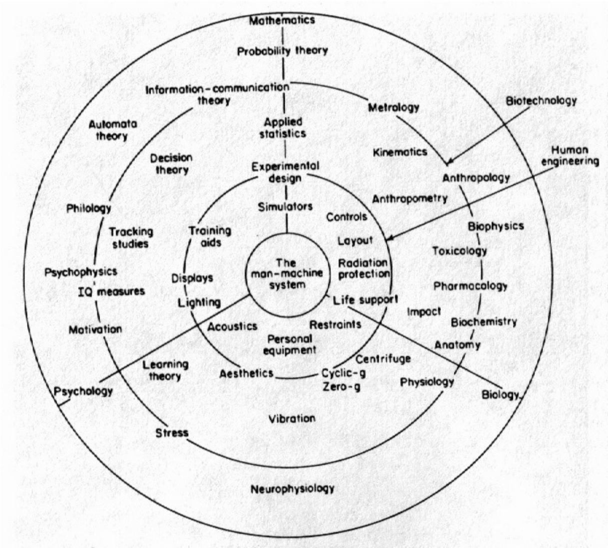
Institutionalizing the engineering of nature

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 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. The Swedish Academy opened a section of *biotecnik* in 1942.

U.S. engineering concept of biotechnology, 1963



SCIENCE

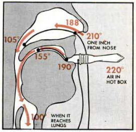
AS THE TEMPERATURE IN HIS HOTBOX RISES ABOVE 220°, DR. TAYLOR SQUIRMS IN HIS SEAT WHILE BEFORE HIM AN EGG ON A METAL PAN FRIES IN THE HEAT

HOW HOT CAN A MAN GET?

Tests show humans can stand heat 50° above boiling point of water

What happens to a human placed in an oven hot enough to cook an egg? The oddly equipped man above, Dr. Craig Taylor of the University of California at Los Angeles, is finding out in an experiment extremely important to modern aviation. In the present 600-mph jet-propelled planes, air compression and friction make the cabin almost unbearably hot when the refrigeration system fails. In even faster planes, the heat increase might be great enough to turn the pilot's cabin into a furnace. Because men are needed to fly these fast planes, the Air Force therefore must know just how much heat a pilot can stand and for how long without suffering either skin burns or internal injury.

Dr. Taylor has exposed himself to temperatures as high as 262°F. He once endured a 220°F temperature for 25 minutes. Except for a temporarily increased pulse rate, the tests produced no serious effects. The heat-recording thermocouples connected to his head and body show why (*drawing at right*). Because the body has its own cooling system (perspiration and mucous secretion), it lowers almost to body temperature all air coming into the lungs. And even when exposed to extreme heat the body does not let its own temperature rise more than one or two degrees above normal.



TEMPERATURE DROPS rapidly before air enters the lungs, as shown in drawing of the nose and throat above.

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Craig Taylor, Professor of biotechnology, University of California Los Angeles, at work

Time magazine article

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 in beans.
- Biogas and gasohol: In rural 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 the 1950s, the oil companies developed processes for growing bacteria on oil. In 1968, the Japanese produced 110 tones of single-cell protein bacteria.

Quorn, a food product made with mycoprotein

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 by Watson and Crick, 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 a small amount of DNA to produce a large 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 every 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–) carried out a collaborative project at Stanford University and University of California at San Francisco. Boyer had been studying *EcoRI*, which cuts DNA in such a way that the ends were staggered, so that one severed piece latches onto another piece possessing a complementary cut. Meanwhile, Cohen had been studying plasmid DNA in *E. coli* and shown they replicate independently of the bacterium's 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.

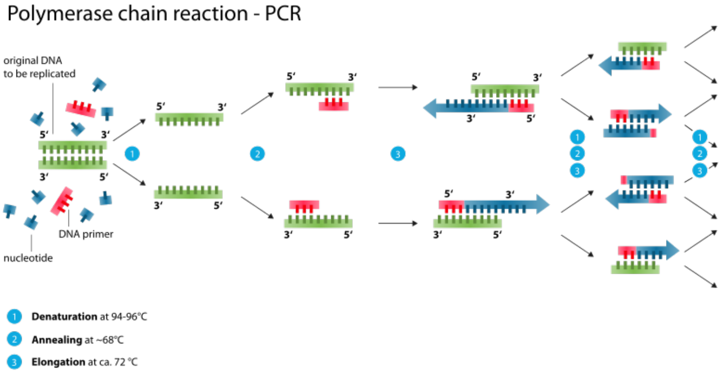
They then went on to show that genes could be spliced into an organism of a different species using similar techniques.

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.

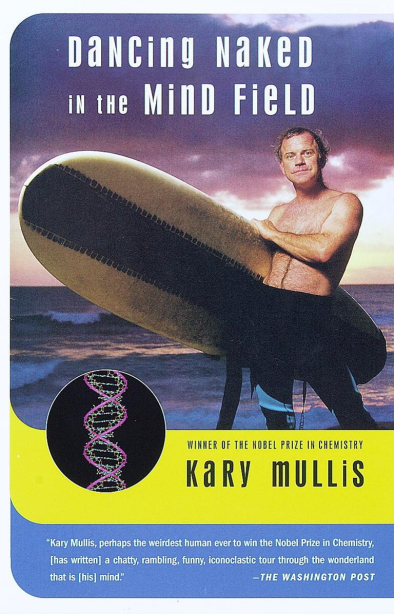
The idea was to heat up the solution of DNA to cause the strands to separate – to denature – and then cool it and mix it with primers – pieces of DNA that begin the sequence one is interested in copying – and then warm it a bit so that new strands form following the primers. This process is then repeated 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.



The 1980s: Technological developments

- In 1980, The U.S. Supreme Court (SCOTUS), in Diamond v. Chakrabarty, approves the principle of patenting genetically engineered life forms. In the same year, a U.S. patent for gene cloning is awarded to Cohen and Boyer.
- In 1982, Humulin, Genentech's human insulin drug produced by genetically engineered bacteria for the treatment of diabetes, is approved by the Food and Drug Administration (FDA). This is followed by many new drugs based on biotechnologies.
- In 1984, the DNA fingerprinting technique was developed.
- In 1989, microorganisms were used to clean up the Exxon Valdez oil spill.

The 1990s: Technological developments

- In the 1990s, a growing number of drugs, produced using modern biotechnological techniques, were brought to market.
- In 1993, The U.S. Food and Drug Administration (FDA) declares that genetically modified (GM) foods are “not inherently dangerous” and do not require special regulation. GMOs are now widely available, but there is still a debate about labeling.
  - Calgene’s Flavr Savr tomato, engineered to resist rotting, was approved for sale by the FDA.
- In 1997, Scottish scientists report cloning a sheep, Dolly, using DNA from adult sheep cells. (Dolly was euthanized in 2003.)
- In 1998, human skin was produced in vitro.

Patenting life

- As mentioned, in 1980, the U.S. Supreme Court approved the principle of patenting genetically engineered life forms. There was resistance in Europe and Japan, but this was later broken down. In the same year, U.S. patent for gene cloning is awarded to Cohen and Boyer.
- This has lead to the ability of technoscientists to patent the genes that they construct using rDNA techniques. This gave them legal ownership of these genes and allowed them to extract fees for use and distribution.
  - In 1992, James Watson stepped down as head the Human Genome Project over conflicts with Bernadine Healy (head of the NIH) over patenting gene sequences, when the NIH announced that they would seek to patent certain human genes.
  - The right to patent genes was struck down by SCOTUS in 2013.

Genetically modified organisms (GMO) and foods

- Using rDNA techniques in GMOs produce can various effects:
  - Resistance to herbicides, resistance to pests and diseases, higher nutrient loads, etc.
- In 1993, the 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 10 years.
- The use of genetically modified crops is protected by license (similar to software), which makes these crops prohibitively expensive for many farmers.
  - Recently, Monsanto charged Argentinian farmers license fees when they tried to sell their GM crops in Europe.
- One major concern with GM crops is “gene flow,” in which GM crops begin to “contaminate” the nearby crops or the wild populations.
  - There have been cases of organic crops becoming “contaminated” with GM organisms.

Overview

- We discussed the application of scientific methods to the brewing and fermentation industries in the late 19th and early 20th centuries.
- We discussed the development of the concept of biotechnology and some of the early projects of WWI.
- We covered the rise of philosophies of biotechnology in the interwar period.
- We looked at the wartime production of penicillin as an example of a new mode of doing science.
- We looked at the rise of biotechnology as an industry and some of the key events in the development of genetic engineering.