

A History of Biotechnology

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

What is biotechnology?

Although the concept of biotechnology generally brings to mind genetic engineering, it can be conceived of very broadly.

Definition (Biotechnology)

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

- In this way, we can trace the history of biotechnology from the beginning of scientific agriculture and fermentation at the end of the 19th century.
- Throughout the 20th century, there was both much hope for, and much disappointment in, the development of biotechnology.
- By the last decades of the 20th century, biotech became a major component of the R&D of most developed nations.

Zymotechnology

- Zymotechnology is the old 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.
- Of course, these practices go back to ancient times, however, in the 19th century, with the rise of big industries, particularly in Britain and Germany, technoscientists began to isolate the microorganisms involved and to study them.
- With the techniques of scientific biology of the 19th century, 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 these products.
- In this regard, at the end of the 19th century, various industrial and governmental labs, and teaching institutions were established.

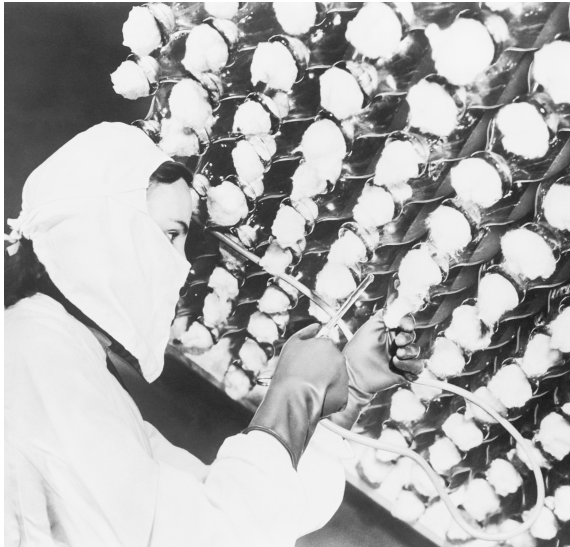
Early biotechnology

- In the early part of the 20th century, technoscientists began to see zymotechnology as included in the applied sciences, analogously to chemistry. They established institutions for collecting and studying microorganisms.
- The concept of zymotechnology was broadened to a general concept of biological chemistry, involving the use of biological molecules such as amino-acids, proteins and enzymes in industrial production.
- The word 'biotechnology' was coined by Karl Ereky (1878–1952), in Hungary in 1919, to describe general processes of converting raw materials into useful products, such as on industrial farms.
- In Britain, Chaim Weizmann (1874–1952) developed bacterial fermentation processes for producing organic chemicals such as acetone and cordite propellants. During WWII, he worked on synthetic rubber and high-octane gas.

World War II: Penicillin production

- In 1928, Alexander Fleming (1881 –1955) accidentally discovered the properties of the penicillium fungus, but determined that it would not be possible to use it in medicine.
- In 1940, a team of researchers at Oxford University found a way to purify penicillin and keep it stable.
- Pfizer, which had made fortunes using fermenting processes to produce citric acid in the 1920s, turned its attention to penicillin.
 - The company developed a complicated production process and opened a new factory 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.

Penicillin production, 1944



Penicillin advertisement, Yaws in Africa

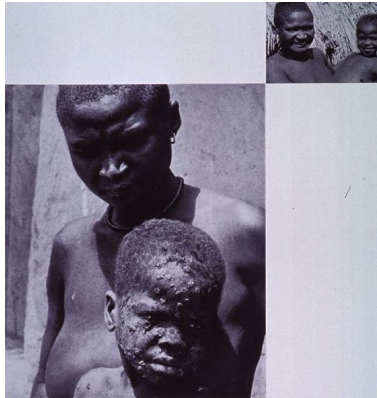


Photo: Eric Schmitt

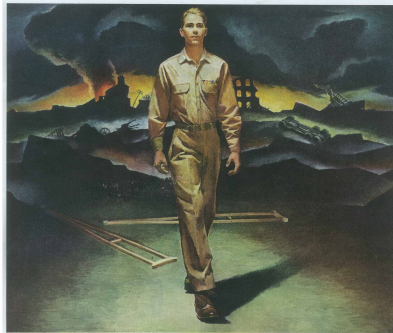
PENICILLIN CURES THIS DISEASE

This hideous affliction is called yaws. A single shot of penicillin will cure it. By the end of 1958 national teams assisted by WHO and UNICEF had treated 25 million such cases.

WORLD HEALTH ADVANCES - WHO Picture Set No. 2

5

Shell penicillin advertisement, WWII



A Prayer Is Answered

Shell Research opens the way to great increases in production of the miracle drug **PENICILLIN**

PENICILLIN has been called the "miraculous single drug ever known to mankind." The need for the drug—in human forms 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 is a "leech" by the parent mold, was unstable—quickly became inactive in handling—and was extremely difficult to "freeze" from the broth. Despite efforts of many scientists, up to half of the drug was being lost.

This was plainly an intricate problem—and a tough one. Shell's special ability in this field has long been recognized, as a result, the possible recovery problem was brought to Shell Research.

Although it was off the beaten track of penicillin research, it had a familiar sound. Here the need was to "freeze" something being lost. For many years, Shell scientists have been deeply

busy separating and recovering "lost" elements from the complex molecular structure of petroleum—such as the materials necessary to make 700 airplane engines, or to make for TNT. They went to work on samples of penicillin broth.

Shell's, after intensive research, Shell developed a new recovery process for the action of which production of penicillin could be substantially increased in some plants now disabled.

Since penicillin is full-scale production, today 2 producers of penicillin have in operation—on under construction—recovery plants of Shell design.

Shell is grateful for the opportunity to bring its research discovery to the great cause of healing. No other Shell company problem or sale, penicillin, although Shell experts supervise the design and construction of new plants using the Shell process, and oversee their initial operation.

Lead in the research freedom for greater profits and abundance. In their own field of penicillin research, Shell scientists have made striking contributions to the war. These will "carry over" to your post-war recovery—in new facts and habits for your life—really when the world starts.

For immediate action: Shell's Research and Development Department, P.O. Box 1000, London, E.C. 4, England.



Engineering nature: various visions

- 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

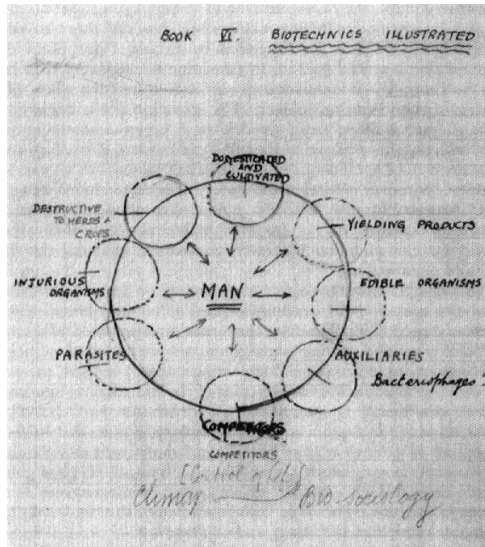
R. Francé, *Plants as Inventors*, 1920:

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.

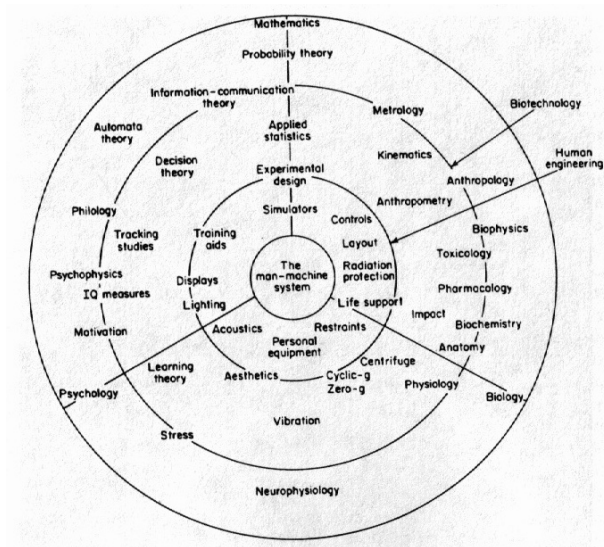
Patric Gedde's construction of biotechnics, notes



Institutionalizing the engineering of nature

- After WWII, technoscientists began to **institutionalize** biology and biotechnology in various ways; that is, to establish departments, institutes and ministries.
- During the war, a number of countries had used biotechnological means to supplement their shortages. These techniques were now institutionalized.
- Cybernetics and general systems theory began to explore the parallel structures of machines and biological systems. That is, they began to explore the general theoretical similarities between biological and technological systems.
- At MIT there was already a department of biological engineering (1936). 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.

U.S. engineering concept of biotechnology, 1963





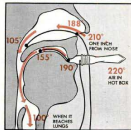
AS THE TEMPERATURE IN HIS HOTBOX RISES ABOVE 100°, DR. TAYLOR SQUIGGLES IN HIS SEAT WHILE BEFORE HIM AN EGG ON A METAL PAN FRIGS IN THE HEAT

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 facing out in an experiment, extremely important to modern aviation. In the present 50thousand jet-propelled planes, air compression and friction make the cabin almost unbearably hot but for the refrigeration system fails. In even faster planes, the heat increase might be great enough to turn the pilot's valves 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 with-

out suffering either skin burns or internal injury. Dr. Taylor has exposed himself to temperatures as high as 262°F. He once endured a 230°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 secretions), it forces about its 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, prof. 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 as an alternative to a list of earth-destroying technologies developed by the “military-industrial complex.” It was hoped that it 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 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, Japan produced 110 tones of single-cell protein bacteria.

Quorn, a food product made with mycoprotein



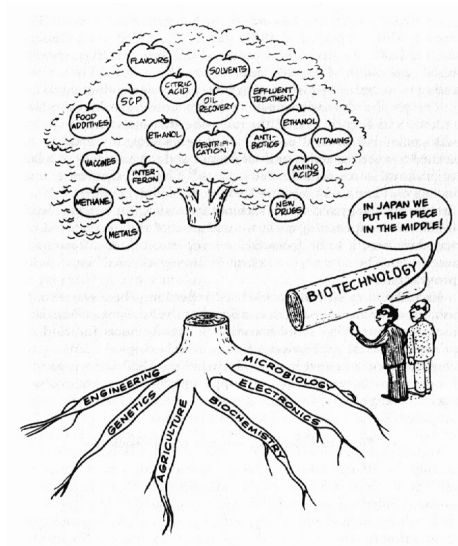
Early biotech policy: Japan

- Japan's long history of the use of fermentation processes (発酵, 醗酵) gave Japanese technoscientists a broad conception of biotechnology.
- In the 1970s, Japan became a world leader in biotech policy.
 - By the end of the 1960s there were serious pollution problems (公害問題), and this led to the idea that biotechnology could be used to make environmentally sound technologies.
- In the 1970s, the Ministry of International Trade and Industry (MITI, 通商産業省) put special emphasis on life sciences and biotechnology.
 - *White Paper on S&T*, 1977: "Life Science, in particular, is for the study of phenomena of life and biological functions that will be made useful; for industrial, medical, agricultural and environmental purposes, and so this area of science is expected to set the pace for the next round of technical progress."

Early biotech policy: Germany and Britain

- In the 1960s the Germans also became concerned with environmental protection (*Umweltschutz*) and began to put emphasis on a new mode of development.
 - Symposium of Industrial Microbiology, 1969: “A future aim should therefore be to close the gaps by suitable training, to rise above classical fermentation technology, and to build up a modern science of biochemical-microbiological engineering.”
- In Britain and the US, chemical engineering the antibiotics industries and applied microbiology developed rapidly.
- In 1979, a British government report outlined the country's policy on biotechnology, which it defined as “the application of biological organisms, systems of processes to manufacturing and service industries.”
 - The British generally followed the Japanese and German policies, however, they put more emphasis on genetic engineering.

Cartoon from the *New Scientist*, 1979



The new genetics: Tatum and Lederberg

In the 1970s-80s, the path of biotechnology became intertwined with that of genetics.

- Edward Tatum (1909–1975) and Joshua Lederberg (1925–2008) shared the 1958 Nobel Prize for showing that genes regulate the metabolism by producing specific enzymes. They both did a great deal to advocate the use of genetics to biological engineering.
- At a conference in 1964, Tatum laid out the vision of the new biotechnology:
 - “Biological engineering seems to fall naturally into three primary categories of means to modify organisms. These are:
 1. The recombination of existing genes, or eugenics.
 2. The production of new genes by a process of directed mutation, or genetic engineering.
 3. Modification or control of gene expression, or to adopt Lederberg’s suggested terminology, euphenic engineering.”

Recombinant DNA technology and monoclonal antibodies

- In 1974, Stanley Cohen (1922–) and Herbert Boyer (1936–) developed a technique for splicing together strands of DNA from more than one organism. The product of this transformation is called *recombinant DNA* (rDNA).
- This technique, for the first time, allowed the genetic engineering of new organisms.
- *Monoclonal antibodies* are antibodies that are clones made from a single immune cell. Antibodies are specific to a given antigen (a disease causing agent), so monoclonal antibodies are used to engineer targeted medicines.
- Techniques for producing monoclonal antibodies were developed in 1975.

Public concern

- The technical progress of genetics, in the 1960s, led to an increasing public concern about the ethics of biotechnology and the possibility of blurring the definition of 'human.'
- In 1975, there was a conference at Asilomar, attended by scientists, lawyers and physicians, to set out guidelines for experiment design and safety, in order to reduce biohazards.
- In 1976, a moratorium on genetic research expired and the U.S. National Institutes of Health (NIH) published guidelines on good practice.
- Amid growing concerns from the general public, in the late 1970s, industrial research in genetically based biotechnology began to expand rapidly with the establishment of many new companies and the development of new techniques.

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 was followed by many new drugs based on biotechnologies.
- In 1983, Kary Mullis develops polymerase chain reaction (PCR), which allows a piece of DNA to be replicated over and over again.
 - In 1984, the DNA fingerprinting technique was developed.
- In 1989, microorganisms were used to clean up the Exxon Valdez oil spill.

The 1980s: Policy in Japan, the U.S. and Europe

In the mid-1980s, the developed nations each spent around \$100m a year on biotech R&D.

- In 1981, MITI (通商産業省) identified biotech as a key industry of the future. Policies for rDNA technology were developed and by the late 1980s corporate biotech R&D was more than doubling every year.
- The U.S., envious of the growth in Japan, was forced by local customs to focus more on basic research than industrial applications.
- In Europe, international agencies were established to promote and regulate biotech R&D, and to try to bring the agricultural and industrial sectors closer.

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.

Confusion and alarm

- The new technologies are rarely understood by journalists or the public at large, but there was, and remains, a vague feeling that something is not right.
- As an example, we can consider the milk-producing hormone, recombinant bovine growth hormone, or somatotropin (rBGH, rBST).
 - rBST is a chemical hormone that is produced using rDNA manipulated bacteria and then fed to normal cows.
 - One article read, “In other words, do you want your milk to come from Daisy or a genetically engineered and manipulated machine?”
 - The U.S. is the only developed nation that allows the use of rBST in milk production. It was banned in most other countries around 2000.

Opposition and resistance: Japan, the U.S. and Germany

- The technical successes of the 1980s–90s, lead to even greater concerns about the long term repercussions of biotech.
 - *Bio/technology*, 1989: In Japan, “77% of the readership of the science magazine *Newton* predicted that biotechnology will develop into the same sort of social problem as atomic energy.”
- In the U.S., people who were uncertain about the long term repercussions of biotech sought to stop the release of genetically modified organisms through the court systems.
 - In 1982, two professors at U.C. Berkeley sought permission to test a bacterium called “Ice Minus,” which would inhibit the frost on strawberry plants. This was contested in the courts.
- In Germany, a very strong environmental movement sought to address the new biotech on a number of fronts.
 - Gen-ethic Network: “We must develop a new ethic for dealing with our knowledge and cannot entrust this task only to scientists, politicians and so-called experts, nor can we leave it to the mechanisms of the free market.”

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 *scientism* and *technological determinism*, 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 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 20 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 “genetic drift,” 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.

GM crop production worldwide, 2015

Countries growing genetically modified crops



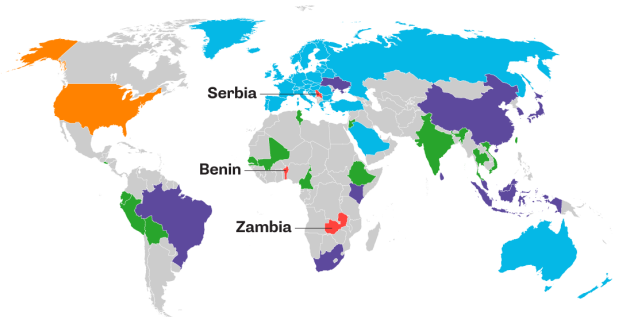
Fuente: isaaa.org (International Service for the Acquisition of Agri-biotech Applications) | 2015

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Countries that label GM foods, 2016

GMO Food Labeling Laws Around the World

- GMO food banned
- Package labeling required for **nearly all** GMO food
- Package labeling required for **some** GMO food
- Limited or weakly enforced labeling requirement
- Labeling requirement yet to come into force
- No GE food labeling law





In 2003, TK-1 (GloFish) went on sale in Taiwan, as the first genetically modified pet.



In 2006, the artist Stelarc had an ear grown in a vat and grafted onto his arm.



In 2009, Sasaki and Okana produced transgenic marmosets that glow green in ultraviolet light — and pass the trait to their offspring.

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 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 will be used to modify the 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 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. M. Shkeli, +%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 breaching protocol.
- Big Pharma is very powerful internationally, and have 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 come to be seen as a major key to economic development.
- We have seen that there 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.