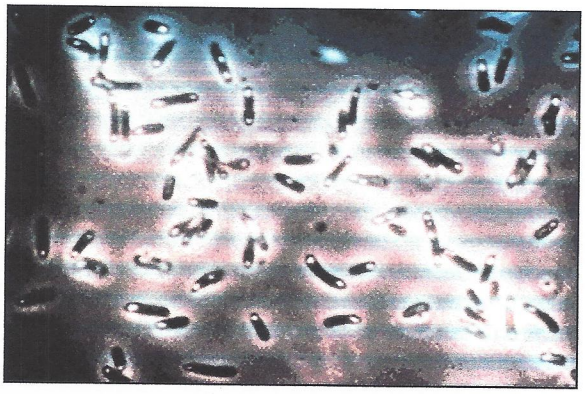
Microbial Fermentations: Changed The Course Of Human History



Localized protein deposits inside rod-shape E. coli bacteria(X2000). by Genentech, Corporate Communication

Christine Case, Ed.D.
Microbiology Professor, Skyline College

When people find out that I'm a microbiologist they frequently ask how I live: "Is your house scrupulously clean? Do you sterilize everything? How do you avoid microbes?" Undaunted by questions concerning my house-cleaning, I enjoy providing examples of the importance of microorganisms in our daily lives and the myriad of foods and drugs that microbes produce. I know that microbiological discoveries have played an important part in the course of human history, contributing to advances in health, nutrition, and use of environmental resources. I was captivated and amazed, however, to learn that microbiology was instrumental in the origination of an entire country and that a microbiologist was elected a nation's president.

My training and research experience is in industrial microbiology, where microorganisms are put to work to make a product. Fermentation is an important part of industrial microbiology. Fermentation technology got its origins the first time someone made wine, was perfected in the 1940's with the production of antibiotics, and is the now the primary method of production in the biotechnology industry.

What Is Fermentation?

Fermentation has always been an important part of our lives: foods can be spoiled by microbial fermentations, foods can be made by microbial fermentations, and muscle cells use fermentation to provide us with quick responses. Fermentation could be called the staff of life because it gives us the basic food, bread. But how fermentation actually works was not understood until the work of Louis Pasteur in the latter part of the nineteenth century and the research which followed.

Fermentation is the process that produces alcoholic beverages or acidic dairy products. For a cell, fermentation is a way of getting energy without using oxygen. In general, fermentation involves the breaking down of complex organic substances into simpler ones. The microbial or animal cell obtains energy through glycolysis, splitting a sugar molecule and removing electrons from the molecule. The electrons are then passed to an organic molecule such as pyruvic acid. This results in the formation of a waste product that is excreted from the cell. Waste products formed in this way include ethyl alcohol, butyl alcohol, lactic acid, and acetone--the substances vital to our utilization of fermentation.

Lactic Acid Fermentation

During lactic acid fermentation, the electrons released during glycolysis are passed to pyruvic acid to form two molecules of lactic acid. Lactic acid fermentation is carried out by many bacteria, most notably by the lactic acid bacteria used in the production of yogurt, cheese, sauerkraut, and pickles. Some animal cells such as muscle cells can also use fermentation for a quick burst of energy.

Alcohol Fermentation

Alcohol fermentation also begins with glycolysis to produce two molecules of pyruvic acid, two molecules of ATP, and four electrons. Each pyruvic acid is modified to acetaldehyde and CO2. Two molecules of ethyl alcohol are formed when each acetaldehyde molecule accepts two electrons. Alcohol fermentation is carried out by many bacteria and yeasts .

Fermentation in Industry

In industry, as well as other areas, the uses of fermentation progressed rapidly after Pasteur's discoveries. Between 1900 and 1930, ethyl alcohol and butyl alcohol were the most important industrial fermentations in the world. But by the 1960s, chemical synthesis of alcohols and other solvents were less expensive and interest in fermentations waned. Questions can be raised about chemical synthesis, however. Chemical manufacture of organic molecules such as alcohols and acetone rely on starting materials made from petroleum. Petroleum is a nonrenewable resource; dependence on such resources could be considered short-sighted. Additionally, the use of petroleum has concomitant environmental and political problems.

Interest in microbial fermentations is experiencing a renaissance. In 1995, J. W. Frost and K. M. Draths wrote that "chemistry is moving into a new era" in which renewable resources and microbial biocatalysts will be prominent. Plant starch, cellulose from agricultural waste, and whey from cheese manufacture are abundant and renewable sources of fermentable carbohydrates. Additionally these materials, not utilized, represent solid waste that must be buried in dumps or treated with waste water.

Microbial fermentations have other benefits. For one, they don't use toxic reagents or require the addition of intermediate reagents. Microbiologists are now looking for naturally occurring microbes that produce desired chemicals. In addition, they are now capable of

engineering microbes to enhance production of these chemicals. In recent years, microbial fermentations have been revolutionized by the application of genetically-engineered organisms. Many fermentations use bacteria but a growing number involve culturing mammalian cells. Some examples of products currently produced by fermentation are listed in Tables 1 and 2 .

How Does Fermentation Work in Biotechnology?

In the pharmaceutical and biotechnology industries, fermentation is any large-scale cultivation of microbes or other single cells, occurring with or without air. In the teaching lab or at the research bench, fermentation is often demonstrated in a test tube, flask, or bottle-in volumes from a few milliliters to two liters. At the production and manufacturing level, large vessels called fermenters or bioreactors are used. A bioreactor may hold several liters to several thousand liters. Bioreactors are equipped with aeration devices as well as nutrients, stirrers, and pH and temperature controls.

At Genentech, Inc., for example, in order to get a product from fermentation, fermentation scientists develop media and test growth conditions. Then, a scale-up must be done to reproduce the process at a large volume. During production, technicians monitor temperature, pH, and growth in the bioreactors to ensure that conditions are optimum for cell growth and product. Bioreactors are used to make products such as insulin and human growth hormone from genetically engineered microorganisms as well as products from naturally-occurring cells, such as the food additive xanthan.

The products being developed by the biotechnology industry have enormous implications for our future health and well-being. All of the exciting discoveries in current biotechnical research and its applications will, of course, have repercussions within human history. Science and politics have always interacted, in both direct and indirect ways.

Microbiology, Synthetic Rubber, and The Making of a Nation

The uses for rubber were limited until 1898 when John Dunlop used vulcanized (heated or fireproofed) rubber to make automobile tires. The rest, as they say, is history: By 1918, there were more than nine million cars in the United States and the United States was using 50 percent of the world's rubber production. Already, by around 1900, the growing demand for rubber and the desire by countries to be self-sufficient motivated scientists to develop synthetic rubber. The greatest stimulus for development of synthetic rubber, however, was the blockade of Germany during World War I. Faced with a cutoff of its supply of natural rubber, Germany succeeded in manufacturing synthetic rubber by polymerizing butadiene, which is obtained from petroleum or alcohol.

In 1904, Chaim Weizmann was a chemistry professor at Manchester University in England trying to make synthetic rubber. He was looking for a microbe that would produce the necessary butyl alcohol. Weizmann was a Russian-born Jew who was active in the Zionist movement which advocated the creation of a homeland for Jews in Palestine. During his stay in England, he became a leader of the international Zionist movement.

By 1914, Weizmann had isolated *Clostridium acetobutylicum*, a bacterium which used inexpensive starch to produce a high yield of butyl alcohol and acetone. However, World War I broke out in August of 1914 and diverted attention away from synthetic rubber and toward gunpowder (cordite). As it turns out, the solvent for making nitrocellulose and thus cordite was acetone. Weizmann was instrumental in making available a source for the creation of this acetone.

Acetone had previously been made from calcium acetate imported from Germany. Since importation of the German calcium acetate was not possible and the United States did not

have a large supply, Weizmann was recruited by Winston Churchill and the British government to set up his microbial fermentation for the production of acetone from corn at the Nicholson Distillery in London. The grain supply was unreliable, however, because of the German blockade and it was necessary to look for a different fermentable carbohydrate. Food was being rationed so a substrate that could not be used for human food was needed. In 1916, Weizmann even tried to use horse chestnuts collected by children, but the supply was insufficient for a large-scale fermentation. The British turned to other parts of the British Empire and to their allies for a fermentable carbohydrate. Consequently, in 1916, the Weizmann process was moved to a distillery in Toronto (Canada) and another was built in India. In 1917, a plant was set up to ferment corn in Indiana (U.S.).

After the war, when British Prime Minister Lloyd George asked what honors Weizmann might want for his considerable contributions, Weizmann answered, "There is only one thing I want. A national home for my people." Lord Balfour then gave Weizmann 15 minutes to explain why that national homeland should be Palestine. Weizmann was an eloquent spokesman and convincingly stated his case. The result was the Balfour Declaration, which affirmed Britain's commitment to the establishment of a Jewish homeland.

Weizmann went on to make significant contributions to both microbiology and politics. In 1920, he began a long tenure as President of the World Zionist Organization. In the years that followed, he campaigned with great zeal. In 1948, when the United States was going to reverse its decision to support the independent state of Israel, Weizmann used his considerable negotiating skills to convince President Truman that the United States should affirm their support for the new country, leading to the founding of Israel. In 1949, he was elected the first president of Israel.

From microbiologist to President, Weizmann illustrates not only the persistence necessary in both research and politics, but the strange and interesting ways research and politics interact. What further developments will the products of biotechnical research inspire?

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