Biotechnology: Past and Present

UNIT 17

European Initiative for Biotechnology Education

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The European Initiative for Biotechnology Education (EIBE) seeks to promote skills, enhance understanding and facilitate informed public debate through improved biotechnology education in schools and colleges throughout the European Union (EU).

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MATERIALS

Contents

World Wide Web

Few areas are developing as rapidly as biotechnology. So that they can be revised and kept up-to-date then distributed at minimum cost, the EIBE Units are published electronically.

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INTRODUCTION

About this Unit

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The main purpose of this unit is to provide reference material for teachers of the history of biotechnology. There is also a cartoons strip for young pupils.

Many of the EIBE units include some reference to historical aspects of biotechnology. However, if the teacher or student wishes to make a special study of the history of biotechnology based only on the EIBE units, it would be necessary to search through all the units, collect the information together and synthesise it in a coherent way. It would also probably be necessary to find additional information from other sources Therefore, this unit brings together selected aspects in the history of biotechnology to provide a broader picture which the teacher can supplement with relevant parts of the EIBE units.

Biotechnology really began in early times with the development of crafts to solve problems of food production and conservation which, unknown to those involved, depended on the actions of micro-organisms. There followed a phase of scientific and technical improvement (and dreams?) which led to the introduction of the new term 'biotechnology' with a range of different meanings. As progress moved on at an increasingly rapid pace driven by advances in the sophistication of technical methods, the need arose for active interactions between the science and technology and the society which is being affected by them.

Aims

The unit aims:

- to show the origins and different meanings of biotechnology;
- to illustrate the progress made from early times to the present day in the understanding of the science of living matter which enabled biotechnology to be used for solving problems of mankind, through examples from three areas: (a) food production, (b) management of the environment and (c) manufacture of pharmaceuticals;
- to show how biotechnology has built on an increasing understanding of natural processes and advances in science and technology to bring improvements in the quality of life;
- to increase an understanding of the work of biotechnology companies.

Finally, there is a cartoons strip which presents the history of breadmaking from early times to the present day in a form which is suitable for use with young pupils.

Summary

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History and biotechnology

An exploration of the background to the meaning and origins of biotechnology shows that there is no universally agreed definition of or explanation for them. The links between meaning and origins have caused biotechnology to be moulded by cultural factors which, particularly in the present day, involve interactions of science and technology with society.

Case studies

Three case studies have been selected to illustrate the different origins of three biotechnological activities which are still important today: case study A is an example of the use and continuous development of biotechnology in food production from very early times; case study B shows how biotechnology was introduced in the 19th century to meet increasing problems in the environment which influenced the health and prosperity of nations and previously had been dealt with since very early times by using a non-biological, management approach; case study C is an example of the use of modern biotechnology in turning a 20th century discovery which had potential value for health care into commercial reality on a global scale.

A. Making bread

The development of this essential food from the empirical procedures of the earliest applications of biotechnology, to an awareness of the involvement of yeast and to the introduction of the methods of the modern baking industry; an example of food biotechnology through the ages.

B. Supplying clean water

An account of the non-biotechnological management methods used to meet the increasing demands for water as civilisation developed until it became necessary to turn to biotechnology in the form of sewage treatment, an important example of environmental biotechnology, to help in improving the quality and increasing the supply of clean water.

C. Producing penicillin

The history of the discovery of penicillin and the developmental work which took place in several countries and led to its production and use in the Second World War. This is an example of a more recent application of biotechnology in which new techniques were developed and used to combat both a medical and a political problem.

Milestones: looking back

A chronology of some landmarks in the history of biotechnology, showing important events in science and technology and the progress in biotechnology which developed from them in the areas of medicine, food, agriculture, environment, energy and recycling;

Biotechnology on the Internet

Illustrations of an application of information technology for finding out about the biotechnology companies and their products and for keeping up-to-date with current and future developments in biotechnology

Cartoons

In *Saccaromicio and the Invisible Workers*, the bread yeast *Saccharomyces cerevisiae* is depicted as 'Saccaromicio', a fictional character who tells the story of bread-making from the mysterious crafts of the Sumerians, Babylonians and Assyrians to present day techniques of yeast biotechnology.

History and biotechnology

An exploration of the background to the meaning and origins of biotechnology shows that there is no universally agreed definition of or explanation for them. The links between meaning and origins have caused biotechnology to be moulded by cultural factors which, particularly in the present day, involve interactions of science and technology with society.

A flask of growing micro-organisms which convert a particular substance into a useful commodity is generally considered to represent a biotechnological process. But is a cow biotechnology? After all, it changes grass into milk and meat which are used by man. No, it is not. Making bread and wine is either accepted as being part of 'old biotechnology' (as opposed to new or recent biotechnology) or considered not to be biotechnology. These few examples illustrate that different opinions exist about what should be called biotechnology. Some of the opinions are rather intuitive, others more sophisticated. In fact, a person's concept of biotechnology is influenced by many factors including local culture, available skills and level of education.

In Germany the term *Biotechnik* is used to describe what is generally called biotechnology elsewhere. As a consequence the term *Biotechnologie* in Germany is restricted to the scientific aspects. Also, an economist may have a different opinion than a biologist and an historian on whether they consider brewing to be biotechnology. Historical accounts too often include statements such as 'In the past people did not know what they were doing but now we know'. However, it is important to remember that people will be speaking about our knowledge in the same way in a hundred years time.

To provide a framework for this discussion it is important to start with the origin of the term 'biotechnology' and follow how it has evolved, including a consideration of the concept of the term 'natural'.

The meaning of biotechnology

Considering the German meaning of 'biotechnology' as used by Ereky in 1913, there are two widely accepted but differing approaches to the origins of biotechnology, *i.e.* either from the beginning of mankind (beer, cheese, *etc.*; see Case Study A: Making bread) or from very recent times as a consequence of important advances in science and technology. The latter approach is favoured in the USA where Boyer and Cohen in 1973 proposed a concept in which the first achievements in genetic engineering inaugurated a new era in the application of scientific knowledge to the possibility of changing the genetic information of prokaryotic and eukaryotic cells.

What is the correct approach? Is there one? A short account of the origins and evolution of biotechnology might help .

The origins and evolution of biotechnology

Production of cheese, beer, *etc*. had been practised as crafts without a scientific basis since the beginning of mankind (see Milestones: looking back). In the course of time, increased economic demand stimulated the development of better skills such as the 'top' fermentation of beer. Scientific knowledge increased rapidly after the middle of the 19th century and the work of Pasteur and Koch created the foundation for the new science of microbiology. Micro-organisms were recognised, cultivated and used in pure culture.

Industrial fermentation was developed at the beginning of the 20th century. Weizmann's procedure was used during the First World War in Britain for the production of lactic acid by solid substrate fermentation. Later in this period, knowledge of the molecular aspects of life was increasing, thereby enabling scientists to publish papers predicting the use of biological matter to transform nature and to create a bio-industry.

During the Second World War, the large-scale production of penicillin - the 'miracle cure' - became possible through the development of deep fermentation technology, mainly in USA (See Case Study C: Producing penicillin). The production of other antibiotics and other substances followed.

In the 1950's, the primary structure of proteins was first determined with the work on insulin. The double helix structure of DNA was proposed by Crick and Watson in 1953. These discoveries led to the development of molecular biology in the 1960's and genetic engineering techniques in 1973. However, this advance worried some scientists and led them to institute a self-imposed moratorium on research for a year. Soon after foreign genes were introduced into prokaryotic and eucaryotic cells, the large-scale production of hormones such as insulin and the human growth hormone from recombinant cells became possible and new companies were set up to exploit commercial possibilities, *e.g. Genentech* in 1976. More recently, transgenic plants and animals such as Tracey and Polly (*see EIBE Units 9 and 11*) have been produced for making useful products.

This short description shows the breakthrough brought about by genetic engineering and explains why its development is considered by some authorities to be the origin of biotechnology which then continued to develop through other important discoveries such as monoclonal antibodies and genetic fingerprinting. Equally, however, the introduction of deep fermentation technology was another major technological breakthrough in fermentation technology which can also be considered to represent the origin of modern biotechnology. Other scientific or technological advances can be thought of in the same terms.

In conclusion therefore, historical considerations alone do not allow us to establish the origins of biotechnology. To do that, it is necessary to consider the influence of advances in the techniques of science and technology. But if there is no uniformly accepted scientific evidence for a particular origin of biotechnology, how can anyone claim to have a valid opinion? A fact of increasing importance is that the individual citizen has a legitimate right to an opinion which will be determined by many factors including cultural background, role and position in society, level of scientific understanding and philosophical ideas.

Philosophical ideas bring with them the problem of deciding on the relative acceptability of 'natural' and 'unnatural' phenomena. Genetic engineering, for example, is considered by many people to involve the changing of nature and, therefore, they find that particular aspect of biotechnology to be morally and ethically unacceptable.

The concept of 'nature'

In discussing biotechnology, people very often use such phrases as 'crossing the border', 'natural' processes' and 'natural products'. It is not difficult to question the validity of the use of the term 'natural'. Why are fire and electricity, without which modern civilisation would not exist, natural but DNA transfer, which occurs in nature in the soil and between different species, is not? If one points people toward this argument they are, rightly, not convinced because they think of 'natural' in terms of a comfortable feeling rather than involving rational judgement. The coming of modern biotechnology has confronted us with the need to make choices and we are forced to consider what borders we are prepared to cross.

This thought process has been confronted many, many times throughout history. We can only guess at the discussions, arguments, fights and suppression of views that took place with the introduction of the use of fire, taming of animals, removing trees or starting agriculture. Perhaps many developments took place without being widely noticed, just as we suddenly found ourselves totally dependent on electricity. However, there are also examples of hostility between fishermen and peasants from neighbouring villages; also, a major factor in the wars with the Indians in North America was differing ideas about property.

Perhaps many of us feel that we are now living in an era when important and far-reaching decisions have been made or are being made which affect our very existence, *e.g.* nuclear power, genetic modification of crops. However, in the light of history, perhaps there is nothing new in this. It may be that their importance is less than we think because, in the past, equally crucial decisions were made for reasons which were considered to be very good at the time; but, of course, we can only imagine.

Definitions of biotechnology

The purpose of providing a list of various definitions of biotechnology is to help in discussions of different opinions on biotechnology *(see page 10)*.

Activities for students

It is informative for students to reconstruct major historical events and explore how they might be received in the modern world. Changes in agriculture provide a particularly suitable topic because both historical and contemporary information is readily available.

Points for discussion sessions:

- Uses of living material which nowadays are thought to be natural may have been viewed differently in the past.
- Soil is ploughed or otherwise disturbed for growing crops and improving fertility but some nomadic people see this as a sin to the earth: 'One should not scar Mother Nature'.
- Agriculture brought a distinction between land owners ('acres marry acres') and others and gave rise to the feudal system where the descendants of the original rich, horse-owning knights looked down on tenant farmers.
- Is it true that most wars were not about rivalries for women, but about safe access to fertile soil and transportation of food?
- The reasons for the introduction of innovations in agriculture (such as an organised approach to agriculture, the invention of the plough, selecting seeds, and genetic crossings) and the effects they had on population density.
- Consideration of the consequences of the introduction of innovations in agriculture on the non-agricultural sections of the economy and community.

Some definitions of biotechnology

	Definition	Example
1.	Using organisms to make useful products	*making bread*
2.	Using organisms to turn something of limited value into a useful product	*cows converting grass to milk, meat and leather*
3.	Using micro-organisms to make useful products	*yeast for leavening bread, making wine and beer; lactic acid bacteria for making sour bread and yoghurt*
4.	Using microorganisms to turn something of limited value into a useful product	*bacteria in sewage treatment; fungi producing antibiotics*
5.	Preserving food with the aid of (micro-)organisms	*making sauerkraut, cheese*
6.	Making products with the aid of (micro-)organisms	*making organic acids, medicines*
7.	Changing part of the DNA of (micro-)organisms to make them more useful	*recombinant bacteria for producing hormones*
8.	Changing part of the DNA of (micro-)organisms for economic reasons	*transgenic herbicide-resistant plants*
9.	Integrated use of biochemistry and enzymology, classical and molecular genetics, microbiology and cell biology as well as process technology aimed at the application of biological processes	*making biological washing powders; producing ethanol by fermentation; sewage treatment; recombinant bacteria for producing insulin; making insect-resistant maize*
10.	Application of biological organisms, systems or processes to the manufacturing and service industries	
11.	Integration of natural sciences and organisms, cells, or parts thereof and molecular analogues for products and services	
12.	Controlled and deliberate application of simple biological agents - living or dead cells or cells components - in technically useful operations, either of productive manufacture or as service operations	
13.	Using biological processes to solve problems and improve the quality of life	

CASE STUDY A

Breadmaking

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The development of this essential food, from the empirical procedures of the earliest applications of biotechnology, to an awareness of the involvement of yeast, and to the introduction of the methods of the modern baking industry is an example of food biotechnology through the ages.

The history of breadmaking

Many centuries before the Christian age, Sumerians, Babylonians and Assyrians made use of yeasts to produce bread, wine and beer. They were unconsciously exploiting the fermentation processes which are essential for making these products.

Cereals have been the basis of human nourishment since ancient times. At first cereals were eaten raw, then toasting was introduced. This was the threshold of the breadmaking process. The instinctive act of mastication suggested the idea of grinding cereal between two surfaces. The result was a flour that formed a smooth dough when mixed with water. The dough was placed on a hot slab and baked - and bread was born! However, the product was unleavened because yeast was not involved. Ciorak, made in India, is an example of this type of bread. But when were the activities of yeast first used?

The first techniques

Remains of pieces of leavened bread found in graves and caverns indicate that the use of the leavening process for breadmaking dates back to the Egyptian civilization in 2600 BC, when bread had a magical significance. Seven varieties of bread have been discovered; some were sweetened with honey, dates, figs, seeds and grapes. The process of leavening was discovered by sheer chance but the circumstances are still a mystery. It symbolized an era of discovery, imagination and research: the invention of the oven and the sieve, improvements in the plough, the building of irrigation systems and the production of bread.

The Hebrews

For Hebrews, bread was important in both food and religious contexts Unleavened wafers, known as 'matzos' were taken by the Hebrews when they fled from Egypt. The religious associations continue to the present day when matzos are prepared as a part of modern Jewish Passover celebrations.

The Greeks

When they migrated to their peninsula in 2000 BC, the Greeks were primarily warriors and shepherds. They had little interest in harvesting because the land, a calcarious rock covered by a thin stratum of humus, contained little clay and could not retain water. However, imported wheat from Egypt and Sicily gave the Greeks an opportunity to learn the leavening process, using grape juice as the source of yeast.

In the 4th century BC, the Greeks began to make bread on a commercial scale during the night. This was probably the origin of the practice that is still a feature of breadmaking today.

The Romans

The Romans learned about breadmaking when they conquered Greece. Bread was so important that its production and distribution were regulated by the State, and bakers, called *pistores*, who were skilled in the leavening process, had special privileges. There were different kinds of bread for every social class - for peasants, slaves, knights and the imperial house. There was even a special bread which was distributed free on the occasion of games in the Roman circuses.

The discovery of yeast

Between the end of the 17th and 19th centuries, a series of independent observations made in various parts of Europe led to the discovery of yeast and an understanding of its activities. Antonie van Leeuwenhoek (1632 - 1723) was the first to see yeast cells, as well as other micro-organisms, by examining specimens through simple microscopes which used lenses that he had made. Later, Cagniard de la Tour (1777-1859), using a compound microscope, observed yeasts in the process of reproduction. At that time it was widely believed that organisms such as insects and worms were created from putrified meat and other dead materials, a process known as 'spontaneous generation'. Although some scientists did not accept this theory and designed experiments that disproved it (e.g. Fransesco Redi (1628-1698) showed that fly larvae did not develop on meat that was protected from flies), the discovery of the existence of yeast and other micro-organisms was used by supporters of the theory as further evidence in its favour. However, several investigators continued to attempt to disprove these arguments. The experiments of Lazzaro Spallanzani (1729-1895), Theodore Schwann (1810-1882), Louis Pasteur (1822-1895) and, finally, John Tyndall (1820-1893) clearly demonstrated that micro-organisms did not develop in nutrient solutions that had been heated, i.e sterilised, and that the heated solutions remained sterile if air (which contains micro-organisms) was prevented from coming in contact with them.

These observations led to the rejection of the theory of spontaneous generation and, more significantly, to the development of basic microbiological techniques that enabled the activities of yeast to be studied in the laboratory. Pasteur knew of the importance of using pure cultures for his experiments. This knowledge enabled him to show that some micro-organsms could live in the absence of oxygen, a component of air previously thought to be essential for life, by using the process of fermentation ("life without air" - Pasteur). He demonstrated that sugar is fermented into carbon dioxide and alcohol (ethanol) by specific yeasts, a fundamental part of breadmaking, but little or no alcohol is produced by respiration, i.e.when oxygen is present. Laboratory investigations with yeast have revealed many other new phenomena including the demonstration by Eduard Buchner (1860-1917) that extracts made from yeast by grinding the cells with sand are also able to cause fermentation. This is how enzymes, the active ingredients of the extracts, were first discovered and the development of modern biochemistry began.

Breadmaking today

At the beginning of the 20th century, with the development of large industrial communities, the industrial production of yeasts specifically for bread making was developed. Biologists made an important contribution by discovering that in the presence of air, yeast produces more carbon dioxide than in its absence. Also, improved methods for isolating strains of yeasts especially suitable for bread leavening were developed, setting the scene for the modern industry of bread making as we know it today.

Ingredients

Flour, water, salt (sodium chloride) and yeast are the basic necessities for making bread. In order to make a good quality product, high quality ingredients are crucial: flour must be freshly ground, water must be at the right temperature and the amount of yeast must be accurately measured. Professional skills are necessary for accurate control of the process: understanding the influence of external factors such as humidity, and temperature, the kneading process and the type of oven are important for the consistent production of good quality loaves.

Flour

Wholemeal flour, refined wheat flour, barley flour, rye flour or Indian corn flour may be used in breadmaking. Wheat flour is in most common use because the quality and the quantity of its gluten content is important in giving a light, crisp and tasty product.

The components of flour that are of importance in bread making are starch, enzymes, simple sugars and proteins.

Grain contains 60 - 68% by weight of starch which is converted to the simple sugars maltose and glucose by amylase enzymes that are also naturally present in the grain. Maltose (a disaccharide) and glucose (a monosaccharide) are fermented by the action of yeast to produce carbon dioxide gas. The carbon dioxide produced by fermentation is retained in the dough and causes it to expand and rise (leaven). Carbon dioxide is retained because of the characteristic sticky and elastic consistency which develops in dough. This is due to the presence in the dough of a naturally occurring protein, gluten. The required consistency develops during a process known as 'conditioning'. The active components of gluten are glutenin and gliadin. Proteolytic enzymes in the grain also contribute to the conditioning process.

Water

Water has several important functions in influencing the quality and taste of bread. It is one of the factors needed for yeast to ferment sugars to carbon dioxide and is also needed for the conditioning process. The water supply should be of good quality and have medium hardness.

Salt

Sodium chloride is added as a solution made in warm water. It has a role in three aspects of breadmaking: increasing the plasticity of the dough, influencing the flavour of the bread and increasing its shelf-life.

Yeast

The primary function of this unicellular micro-organism is fermentation, a biochemical process which takes place in the absence of air, *i.e.* it is an anaerobic process. Carbon dioxide is a major product of the fermentation of the sugars in flour and causes the dough to rise. Alcohol (ethanol) is also produced from fermentation but evaporates during baking in the oven. Yeast enzymes also contribute to the conditioning of dough. Some people consider that yeast is involved in giving bread its characteristic flavour but others believe that other micro-organisms are responsible.

As an alternative to using yeast for leavening bread, it is possible to produce carbon dioxide using baking powder. The sodium bicarbonate in baking powder releases carbon dioxide when made into a solution and heated. However, of course, this is a chemical reaction and not biotechnology.

The baking process

The high temperature of the baking oven kills the yeast, inactivates flour and yeast enzymes, causes the gas to expand, removes volatile products of fermentation and contributes to flavour. The oven temperature also sets the shape of the product by causing polymerisation of the flour starch to a form which gives support to its structure. Thus biotechnology has contributed to the making of a product with the required attributes of volume and shape, crust colour, grain, texture, aroma and taste.

Yeast biotechnology

The formal name of the yeast used for breadmaking is *Saccharomyces cerevisiae*, commonly known as baker's yeast. The production of the large amounts of yeast needed in commercial baking is an industry in itself. If you consider that 5 kg of yeast is needed to leaven 300 kg of flour, it is not surprising that a modern bakery can use 100 kg of yeast per day.

Yeast cultures are grown in large fermenters under aerobic conditions, *i.e.* provided with a good supply of air which provides the oxygen needed for producing high yields of yeast cells. Yeast cells are separated from the culture medium, dried to a paste, or for some purposes to granules, and stored for later delivery to bakeries when needed.

Strains of yeast used for baking have been specially selected for the purpose. Important features are: rapid growth; having stable properties; retaining viability, *i.e.* staying alive, in paste or dried form for reasonably long periods before use; producing carbon dioxide rapidly during leavening. Changes in baking practice require strains to have other features such as retaining viability in dough which is frozen for storage before being required for leavening.

Activities for students

1. Make a list and find pictures or make drawings of different types of bread from various countries, religions and cultures of the world.
2. Find out at what times in history the different breads were eaten, how they were made and who ate them.
3. Explain the religious or cultural significance where appropriate.
4. Make a display of the kinds of bread that are sold in local shops or supermarkets. Find out about their sales, *e.g.* who buys them, the popularity of the different types, changes in sales patterns.

CASE STUDY B

Providing clean water

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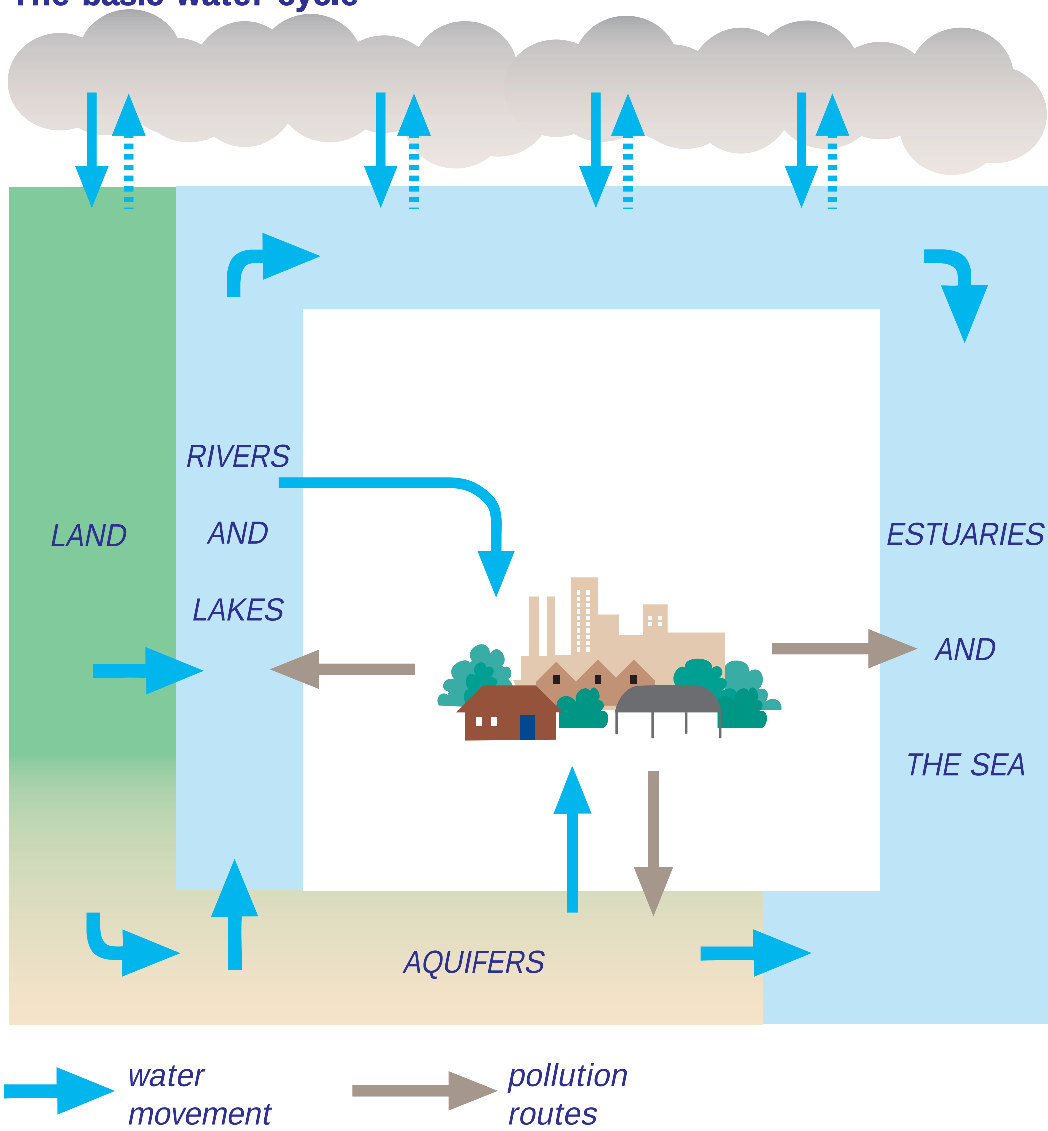
An account of the non-biotechnological management methods used to meet the increasing demands for water as civilisation developed until it became necessary to turn to biotechnology in the form of sewage treatment, an important example of environmental biotechnology, to help in improving the quality and increasing the supply of clean water.

The water cycle

The Earth and its atmosphere contain a limited, constant amount of water which is being continually recirculated within a closed system, the *water cycle*. Solar energy provides the power for moving water around the system.

Water movement occurs naturally through many routes: precipitation; the soil; seas, rivers, lakes and underground streams; transpiration by plants; evaporation and convection. The distribution of water is uneven to the extent that some countries suffer from floods, other from drought; some of the water is in the form of ice which covers 10% of the Earth's surface. Water is extracted and distributed by man for domestic, industrial and agricultural use. The basic water cycle is summarised diagrammatically in Figure 1.

Figure 1. The basic water cycle



Water supply in early times

3000 BC

During the Minoan civilisation, a system of pressure pipes was built in Knossos, Crete to provide clean water for its population of 100 000. There was also a sewerage system of stone drains jointed with cement and the Royal Palace had baths with pottery fittings. There were drains and sewers in Greece (*e.g.* Athens), ancient Egypt and Asia (*e.g.* the Indus Valley).

500 BC

Some towns in Greece had a permanent water supply, fed from water stored in cisterns made from rock.

300 BC

The idea of water systems which had been built in Knossos were developed further in various parts of the Roman Empire. A system of aqueducts for supplying water was built in Gaul (*e.g.* Pont du Gard - Nimes) and Iberia (*e.g.* Segovia, Tarragona). The Marcia and New Anio in Rome were more than 80 km long.

200 BC

Water mills were built by the Greeks and the Norse for providing power.

100 BC

The Vitruvian water mill was developed and aqueducts continued to be built in the cities for supplying water, *e.g.* in Rome there were 9 aqueducts of 500 km total length.

400 AD

In the Dark Ages, the beginning of the fall of Roman Empire led to a return to the insanitary conditions of the Huns and the Goths

1000 AD

There was a temporary renaissance of sanitary conditions towards the end of the Dark Ages but in Norman times it became common practice again in towns to dispose of waste materials into streams.

The response to increasing demand in Britain

1200

In Britain, the water in moats surrounding castles became increasingly polluted by discharges from latrines. The increasing demand for water by the rising population of London led to water being transported in pipes from springs in the surrounding country.

1300

The first stone bridge was built in London over the River Thames in 1307. Houses were also built on the bridge and the occupants disposed of their sewage and other wastes directly into the river. The resulting pollution became a danger because the river was also the source of drinking water. Increasing concern about the dangers to health caused by the rise in pollution led to the building of a system of ditches and drains and the introduction of legislation in the form of the Sanitary Act in 1388.

1500

The population of London rose to 200 000 and consequently greater supplies of food and water were needed. Livestock and other food products were brought in from the country areas and in 1582 the water wheel was first used to pump water from the River Thames. An expansion of industry introduced a greater demand for raw materials and craftsmen which created an increase in the traffic of horses and carts. Instead of returning with empty carts, it made economic sense to use the return journey to take products back to the markets and remove some of the dung which was accumulating from the increasingly large numbers of horses and cows and causing a nuisance.

1600

Rivers such as the Fleet became so polluted that they functioned as open sewers. The water became so unpleasant that it was necessary to take clean drinking water from suitable parts of the River Thames and find ways of transporting it to the inhabitants. In 1610, wooden pipes made of elm were introduced for this purpose; lead pipes were also used.

1700
The Industrial Revolution in Britain and continuing rises in population made even greater demand for water but rivers were not suitable sources because they were used as large drains by homes and industry. People with enough money were able to buy water from travelling watermen and water carts. Then the invention of the steam engine in 1712 made it possible for water to be pumped to fountains and standpipes in towns, thereby making it more widely available to the general public. Hygiene in the home was improved by introduction of the water closet which had been invented in 1590 but not widely used until 100 years later.

1800
In 1840, the daily volume of water used in homes and on farms in Britain was 18 litres per person. This was obtained from wells, streams and rivers in country areas but in towns and cities the pollution of water supplies was still a problem. Sewage flowed along the streets in London, added to by overflows from the cesspools of better class housing, and brought increased dangers to health. Cholera was first reported in Britain in 1831 and 0.25 million people died from the disease in 1848-1854. However, successful steps began to be taken to combat the problem and many changes were brought about through legislation, e.g. Public Health Acts 1848, 1875; Metropolis Act 1852; Sanitary Act 1866.

Open ditches were so unpleasant in appearance and smell that they were covered over which made them into sewers. Overflows from cesspools were reduced by pumping sewage into the sewers using hand pumps and in 1847 it was made compulsory in London for house drains to be connected to surface water channels made of stone. Iron pipes came into use for supplying water to pumps in the streets.

In 1853, a decision was made to take water from cleaner areas of the River Thames further upstream. The effect was a reduction in deaths from cholera in London from 130 to 37 per thousand people. One of the outbreaks in London in 1854 became very famous. There had been more than 500 deaths from cholera in 10 days from the use of a contaminated pump in Broad Street until Dr John Snow prevented people from using the pump by removing the handle and the outbreak ceased.

Special areas of land were allocated for the disposal of sewage and the unpleasantness of the smells which arose from this practice was sometimes alleviated by adding carbolic acid which reduced putrefaction. Incidentally, it was this use of carbolic acid which gave Joseph Lister the idea for aseptic procedures in surgery. Another approach was to make use of the fertiliser value of sewage for agricultural purposes on what were known as sewage farms.

As a result of these various improvements, cholera was eradicated in 1868 but it was almost another 20 years before Robert Koch isolated the bacteria responsible for the disease.

Water needs today
Modern society makes increasing demands for water. As there is a finite amount of water available to us, it is essential to economise on water useage, control pollution and maximise the amount of water which is suitable for re-entry to the water cycle and eventual re-use. In the UK, each person uses about 360 litres of water per day either directly or indirectly. This is made up of 140 litres in the home and 220 litres on our behalf in factories, hospitals and agriculture. For example, the amount of water needed for making some common products are: 1 tonne of concrete, 450 litres; 1 tonne of steel, 4 500 litres; 1 motor car, 30 000

litres. It is also necessary to maintain large stores of water store to ensure an uninterrupted supply, *e.g.* for London, sufficient for 100 days is maintained in reservoirs.

In most European countries, more than 90% (99% in some instances) of the population is connected to a piped water supply although for countries such as Austria, Greece and Portugal the figure is lower (35-55%). Therefore, large amounts of water have to be available to satisfy the huge demands.

In contrast, the picture is very different in other parts of the world. There are shortages of water in parts of the developing world where some people have to survive on as little as 2 litres per day. Another contrast between the developed and developing world is the relative amounts of water used in the home for different purposes *(Table 1)*.

Table 1. Water useage for various purposes in the home

Purpose	*Useage (%)*	
	Europe	*Bangladesh*
personal washing	*30*	*30*
cooking	*7*	*15*
laundry	*11*	*20*
washing dishes	*13*	*15*
other	*39*	*20*

The role of environmental biotechnology

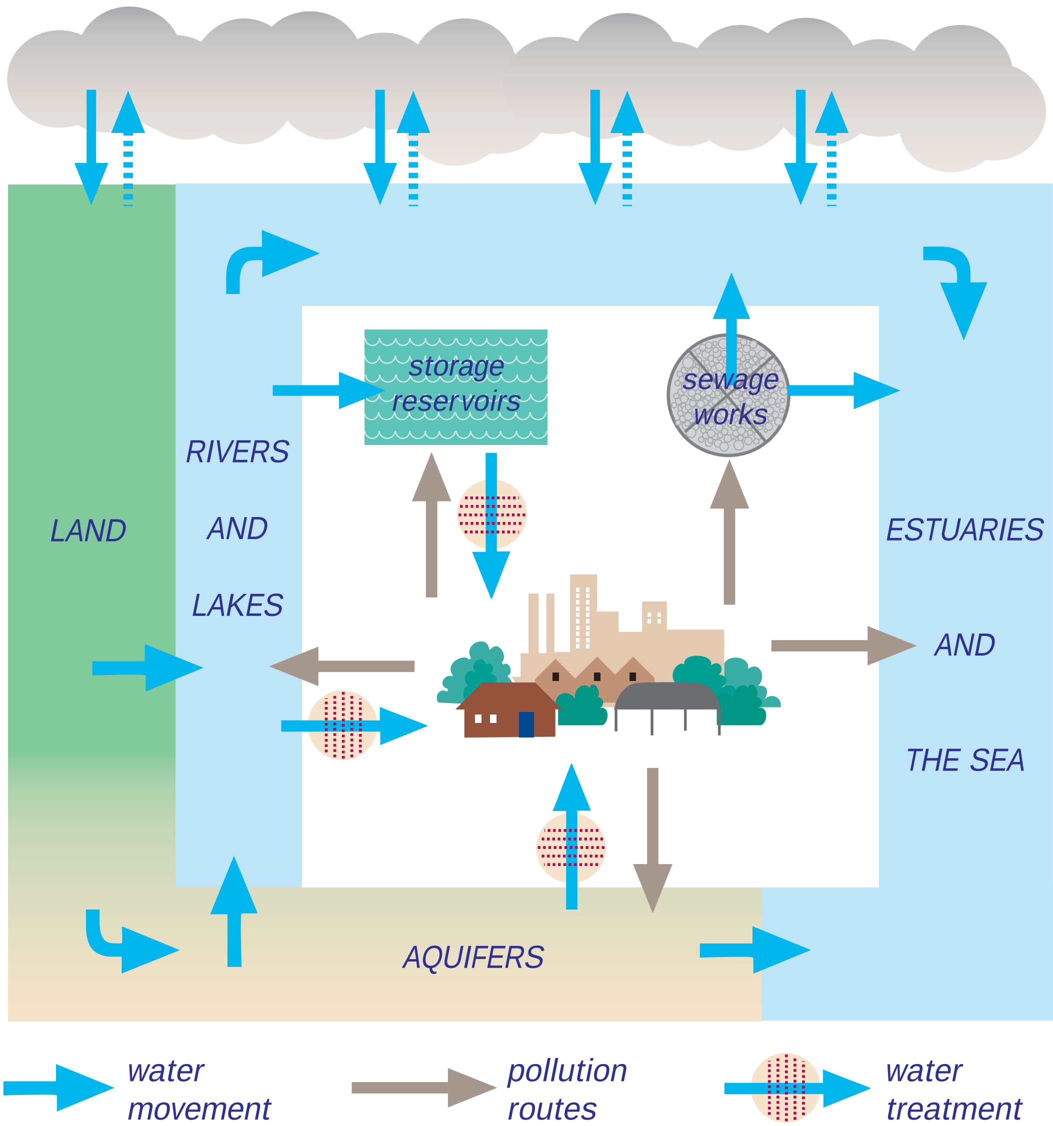
Environmental biotechnology is the application of biotechnology for the protection and restoration of the environment. As with other applications of biotechnology, use was being made of 'environmental biotechnology' long before the term came into use. Systems for the purification of water by filtration and treatment of sewage on a municipal basis were developed in the second half of the 19th century by civil engineers but it was not fully realised that microbiological processes were involved until the 1930s. Gradually, mechanical engineers increasingly worked in collaboration with biologists in the true interdisciplinary spirit of biotechnology to develop improved biological waste systems for dealing with the increasing volumes of polluted water produced by society and industry and to meet their ever-growing demands.

One aspect of the problem still to be addressed in Europe occurs on the Mediterranean coastline. Fifty million inhabitants, excluding the millions more in the summer, produce annually 100 tonnes of sewage per kilometre of coastline of which 85% is disposed of directly to the sea without treatment.

Figure 2 illustrates the routes of pollution arising from increases in population and industrialisation which affect the basic water cycle depicted in *Figure 1*. It also shows the steps taken to maintain adequate water supplies by building storage reservoirs and to ensure the high quality required for consumption and other uses.

Figure 2 also shows that systems for treating effluents from domestic and industrial (including agricultural) sources enable treated water to be returned to the cycle for re-use instead of adding to the levels of pollution in rivers, the sea, *etc*. It is not necessary to describe the process of sewage treatment because details are readily available from other sources. However, a flow diagram of a sewage works is provided in Figure 3 for convenience. The two stages which depend on the biotechnological activities of micro-organisms are (i) secondary (aerobic) treatment and (ii) sludge digestion which takes place in the absence of air (anaerobic) and results in the production of methane gas which can be used for generating electricity.

Figure 2. The water cycle in the 20th century

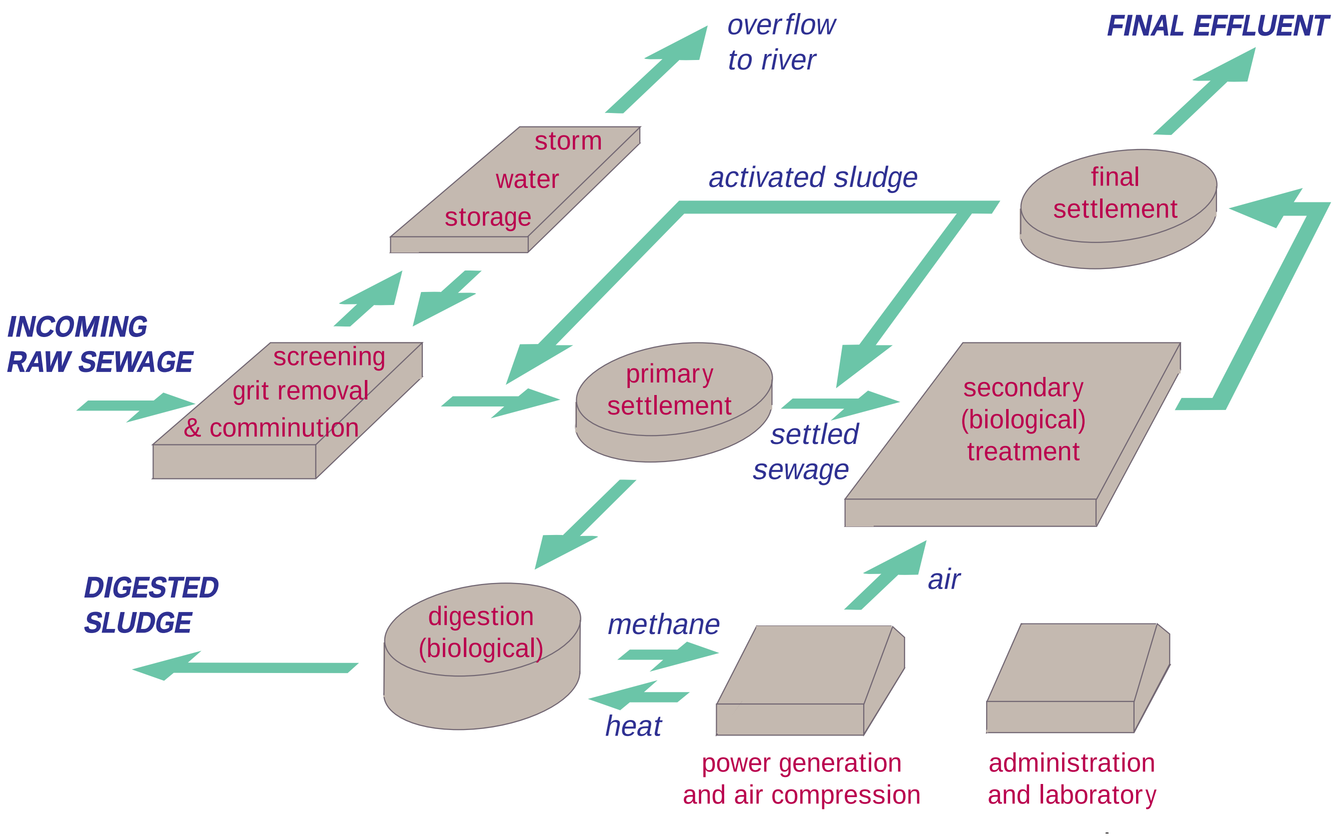


Although the water released from a sewage works is not safe for drinking, the treatment greatly reduces the levels of pollution in the rivers, *etc*. which it enters and also reduces the amount of treatment needed to make water safe for drinking before it is eventually put into the public water supply (see next paragraph).

Supplying safe water

In addition to the *amount* of water needed, attention has to be paid to its *quality* in terms of chemical content (*e.g.* presence of substances which may be poisonous, otherwise influence health or affect taste and smell), physical properties (*e.g.* cloudiness or coloration from solid particles) and biological quality (*e.g.* transmission of disease). In Europe, standards of drinking water quality are controlled by national legislation and EC Directives. Maintenance of supplies which are free from infection is achieved by disinfection with chlorine or ozone, treatments which enable the high levels of quality required to be achieved, *e.g.* 99.5% of samples tested in the UK meet the required standards. However, there is still much progress to be made in the developing world where, for example, 25 000 children every day die of cholera and dysentery from drinking dirty water.

Figure 3. Flow diagram of a sewage works



Activities for students

1. Keep a record of the amount of water used for different purposes in your home for a week. Calculate the annual consumption.
2. Make a table to show the amounts of water being used in various industries in your country.
3. Use information provided by local organisations that provide drinking water and treat waste water to compare the development of municipal processes with that given in the text for Britain.
4. Find out if there are any restrictions on putting waste water into local rivers, *etc.* and, if so, the standards that have to be met.
5. Find out if there are any plans for new housing or industrial developments and the consequences for the disposal of the increased amounts of waste water that will be produced.
6. What are the main problems of water supply in developing countries? Do all developing countries have these problems? What methods are being used in attempts to solve the problems and how successful are they?

CASE STUDY 3

Penicillin production

- the story of a successful World War II programme

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The history of the discovery of penicillin and the developmental work which took place in several countries and led to its production and use in the Second World War. This is an example of a more recent application of biotechnology in which new techniques were developed and used to combat both a medical and a political problem.

Sir Alexander Fleming

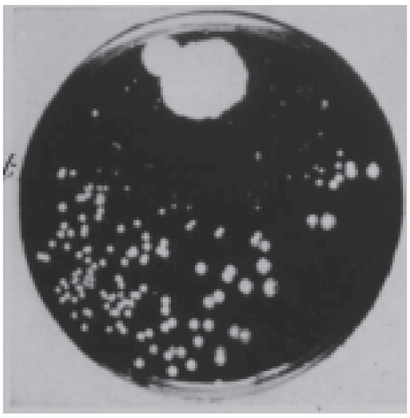
Photo: Wellcome Trust Medical Photographic Library

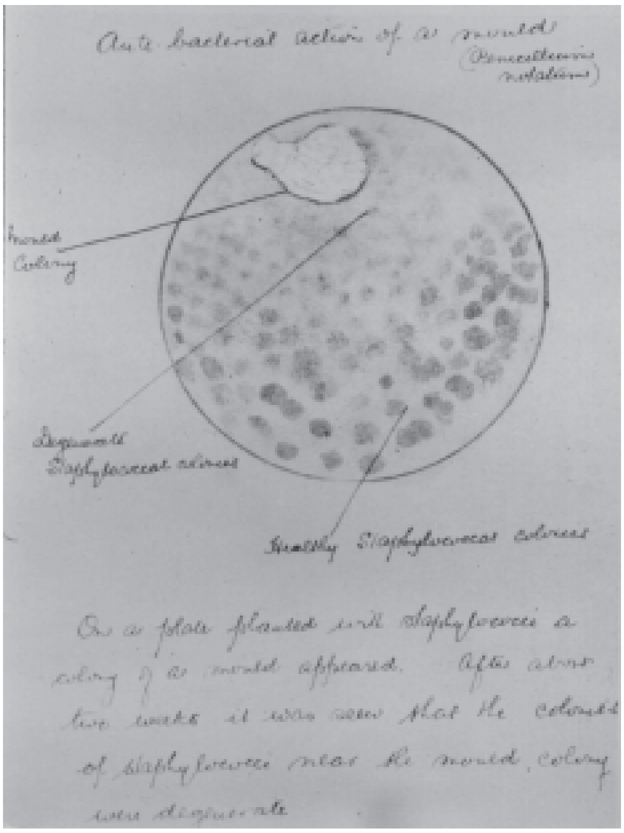
The original discovery

"*Purge me with hyssop and I shall be clean.*" - Psalm 51, v 7.

Even though this passage from the Bible may or may not be the first written reference to the activities of penicillin, there are no doubts about the date of Fleming's momentous observation which led to its discovery. As the story is well documented elsewhere, it is necessary to give only a short summary here. At about 9 o'clock in the morning on a day in September (probably the 3rd) 1928 , Alexander Fleming returned to his laboratory in St. Mary's Hospital in London from a summer holiday. He decided that his first task would be to tidy up his laboratory so he began to remove some of the older cultures of the staphylococcus bacteria in Petri dishes which he no longer needed. As he checked each dish in turn, he suddenly stopped. On one of them, a piece of white

Figure 4. The original mould growth of* penicillium notatum *(below), and Fleming's drawing and notes on its antibacterial action on* staphlococci *(right).





Pictures from the Wellcome Trust Medical Photographic Library mould, an accidental contaminant from the air, had grown near the edge and there were no colonies of the staphylococcus bacterium near it. The mould, later found to be a strain of *Penicillium notatum*, had excreted an inhibitory substance which Fleming called 'penicillin'. The photograph which he took of it was displayed in the British Museum in London *(Figure 4)*.

Fleming and two of his assistants found the best conditions for growing the mould in a meat broth culture medium incubated at room temperature. The mould grew only on the surface of the broth medium because it is a strict aerobe, *i.e.* cannot grow without oxygen which air provides. The liquid beneath the surface layer of mould became yellow and was found to have antibacterial activity. The yellow colour and the antibacterial activity increased as the mould grew. Unfortunately, all attempts at recovering and purifying the active substance failed, even after Fleming had sought advice from his colleague Harold Raistrick, a professor of chemistry. They realised that penicillin is unstable in its unpurified form but they were unable to improve the extraction process.

The rediscovery

In 1938, the Australian Howard Florey, Professor of Pathology at Oxford University in England, and his collaborator Emst Chain, a Jewish biochemist who had emigrated from Berlin in 1933 with his German mother and Russian father, started to look for new bactericidal substances at the Sir William Dunn School of Pathology in Oxford. Chain accidentally saw Fleming's publication on the discovery of penicillin in the course of a literature search which is an essential part of any new research project. Out of scientific interest, they decided to pursue the topic further, without even thinking that it could have any practical use. By the middle of March 1940, Chain had obtained about 100 mg of a brown powder which possessed much higher acivity than Fleming's original mould

Howard Florey

Photo: Wellcome Trust Medical Photographic Library

Ernst Chain

Photo: Wellcome Trust Medical Photographic Library

broth. However, it became evident that only 0.1% of the powder was made up of the antibiotic. Penicillin is not coloured: the brown substance consisted mainly of other products.

No one in the team had any idea at the time about the impact that penicillin, the first antibiotic, was to make to the victory of the Allied forces in Second World War. In May 1940, after tests on a variety of animals had proved that the material was non-toxic, 8 white mice were given a lethal dose of streptococcus bacteria and 4 of them received injections of penicillin. Norman Heatley, another member of the research team who was to play a key role in the work, kept watch in the laboratory through the night. By the next morning, the treated mice were still healthy but the untreated ones were dead. Further successful tests with animals followed and gave the signal for the start of a programme to produce enough penicillin for clinical trials with patients.

The war was not going well for the Allies at that time. British and Allied units were being evacuated to England from Dunkerque on the French coast; Nazi bombs had started to fall on British towns and cities. Therefore, the British pharmaceutical industry was fully committed by the War programme in making vaccines, antitoxins and blood plasma; and consequently, there was no spare capacity for facing the challenge of developing the new fermenter technology necessary for penicillin production. Another obstacle was that the British government had insufficient money available to fund the further research that the groups at Oxford and elsewhere needed to do.

The Oxford researchers calculated that at their current limit of producing 500 dm^3 of mould broth per week, it would take several months for them to obtain sufficient penicillin for treating only 5 - 6 patients. So they quickly turned the laboratories into a small factory. Every conceivable vessel was turned to use for growing the mould - buckets, bathtubs, hotwater bottles, milk-cans, cooling jackets, *etc*. By the begining of 1941 the 'factory" had produced enough penicillin for initial tests on patients but the treatment of the first one, a policeman named Albert Alexander, was a disaster. He had been suffering for two months from septicaemia caused by a streptococcal and staphylococcal infection caused by having scratched his face on a rose bush. Despite massive doses of sulphonamide drugs, he was on the verge of death. Initially, he responded very well to treatment with penicillin but then his condition began to deteriorate and, a month after the first application of penicillin, he died. It had become apparent towards the end of the treatment that the problem was not that the preparation was not active enough; it was simply that not enough material had been produced to complete the treatment. However, better outcomes with other patients followed.

The US enters World War II

In response to the problems encountered in research and development, Florey and Heatley went to the US in July 1941 with the intention of interesting American companies in the large-scale production of penicillin. Officers of National Research Council and the US Department of Agriculture quickly became convinced by the arguments of the British scientists. Shortly afterwards, the government gave Robert D. Coghill of the Northern Regional Research Laboratory in Peoria, Illinois the task of scaling-up the process from the Oxford team's bottle-scale to a large-scale fermentation. It was calculated that with bottle-scale plants, the programme would have needed a row of bottles stretching from New York to San Francisco! In the meantime, Florey had persuaded the US Committee on Medical Research to engage several pharmaceutical companies in penicillin production.

The US officially entered the Second World War in December of the same year. The War Production Board of the US government very quickly recognised the potential value of penicillin for treating war injuries and the programme was declared as 'top secret". The fascinating technical development of the scaling-up from bottles to large fermenters was soon under way, involving many companies, engineering bureaux, universities and administrative offices. Enormous problems had to be solved: the design and the technology of a novel type of a deep fermenter (bioreactor) which could be reliably kept free of contamination during a production run lasting several weeks; optimisation of yield by the selection of better strains of *Penicillium*; development of suitable methods for product recovery and purification. This is where biotechnology was able to show its true nature as an interdisciplinary activity.

Now convinced of the immense possibilities of penicillin, the British Government took the initiative in 1942 and made arrangements for the larger firms of the pharmaceutical industry - *May & Baker, Glaxo, Buroughs Wellcome, British Drug Houses, Boots, ICI, Kemball-Bishop* - to start collaborating in its manufacture. Their engineers went to the US to learn from the progress already made by their counterparts.

Co-ordination by the US administration

In mid-1943, the War Production Board entrusted Albert L. Elder with responsibility for co-ordinating the penicillin programme. He involved scientists from the universities of Minnesota, Wisconsin and Stanford and the Massachusetts Institute of Technology (MIT) with support from the continuing work of Robert Coghill's team in Peoria. They had developed the idea of building large fermenters of up to 100 m^3 capacity with facilities for sterile aeration. These were the first mechanically-stirred tanks.

The Peoria team had also developed corn steep liquor as a fermentation medium, in plentiful supply as a surplus farm commodity and a by-product from the local wet corn milling industry in Illinois. In addition, they had also obtained best penicillin production from a strain of *Penicillinium chrysogenum*, isolated from a mouldy cantaloup melon from a Peoria fruit market. Later, a research group at the University of Wisconsin obtained even better results with an ultraviolet-induced mutant (Q-176) which produced about 1500 International Units of penicillin/ml of culture medium. For comparison, the strain used by the Oxford team of Florey and Chain produced about 3 International Units. After the war, yields were dramatically improved even further, up to 15000 units/ ml.

In the meantime, the company *Gist-Brocades* was independently and secretly developing penicillin production in the Netherlands, then occupied by the Nazis. Their work began in 1943, based on Fleming's publications and information obtained from radio messages. All available strains of Penicillium were tested and one from the species *Penicillium baculatum* was found to be the most promising. As the material produced was different from that with which the British and Americans were working and also so that the Germans would not realise what was going on, *Gist-Brocades* invented the name Bacinol for their product.

By now, many of the pharmaceutical companies in Canada, Britain and, particularly, in the US were producing penicillin. Successful trials took place on infected war wounds in North Africa where, incidentally, penicillin was also found to be very effective in curing cases of gonorrhoea, another hazard to the maintenance of a fully active fighting force. By the time of the D-Day landings on the beaches of Normandy, France which were launched from England in 1944, the Allies were in the advantageous position of having sufficient penicillin available from the US production alone for treating all of the casualties of the Allied invasion of Europe. It can be argued, therefore, that the dropping of atomic bombs on Japan was not the only factor which brought the Second World War to an end.

After the war

This great record of success for penicillin formed the basis for the later world-wide reputations of US pharmaceutical companies such as *Squibb, Bristol, Merck and Co., Pfizer, Lilly* and *Upjohn*. After the Second World War, many manufacturing facilities began to operate in various countries around the world. In addition to the UK, companies were operating elsewhere in Europe, *e.g. Rhône-Poulenc* and *Roussel-Uclaf* in France, *Hoechst* in Germany, *Farmitalia* in Italy, *Gist-Brocades* in the Netherlands (who held an advantage following their clandestine operations during the war), and *Novo* working under licence in Denmark. Increased manufacturing capacities enabled production costs to fall, *e.g.* the price of penicillin in 1965 was 1/10000th of that in 1943.

The phenomenal success of the use of penicillin around the world, the discovery of many other antibiotics and the development of the large-scale fermenter technology which is now a routine feature of modern biotechnology are milestones in the history of biotechnology and mankind. Fleming, Florey and Chain were awarded the Nobel Prize for Medicine and Physiology 1945 for their great scientific achievements.

However, there are always new challenges ahead. Today, there is the very serious world-wide problem of an alarming spread of resistance to antibiotics among pathogenic bacteria - another task being faced by medical biotechnology.

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The life of Sir Alexander Fleming, discoverer of penicillin. By André Maurois, translated from the French by Gerard Hopkins. Jonathan Cape, London, 1959.

Activities for students

1. Write and act a short play about a part of the story of the discovery, production and uses of penicillin.
2. Find out what diseases can be treated with penicillin and the specific microbes which cause them.
3. Find out which diseases cannot be treated with penicillin, why, and how they can be treated.

   (*These two activities could consider different diseases that are caused by bacteria, e.g. sore throats and diarrhoea, recent problems of development of resistance to penicillin, and diseases caused by fungi, e.g. thrush, and viruses, e.g. AIDS.*)
4. In what ways do sulphonamide drugs differ from penicillin?
5. What are semi-synthetic penicillins and why were they developed?

Milestones: looking back

★ ★

A chronology of some landmarks in the history of biotechnology, showing important events in science and technology and the progress in biotechnology which developed from them in the areas of medicine, food, agriculture, environment, energy and recycling.

Date	Some important developments in science and technology	Some important developments in biotechnology
15000 BC		Simple form of fermentation
9000 BC		Alcoholic fermentation, bread, cheese, yoghurt
6000 BC		Beer made by Sumerians
4000 BC		Egyptians use yeast in bread-making and moulds to produce cheese Chinese used mouldy soya bean products for treatment of skin infections
2000 BC - 600 AD		Cultivation of grapes for making wine Improvements in growing crops
1000 BC		Babylonians pollinate date palm trees
400 BC	Hippocrates founded a school of rational medicine in Greece	
320 BC	Aristotle: philosopher and scientist Galenus:	
1100		Distillation of alcohol
1300	Water mills introduced in Europe	.
1521		Aztecs in Mexico harvest algae from lakes for food
1650	Redi rejects spontaneous generation.	Cultivation of mushrooms in France
1670		Commercial production of beer Metal extraction by microbial action
1680	van Leeuwenhoek sees microbes through the microscope	
1727		Founding of *Villmorin- Andrieux*, seed breeding establishment, in France
1752	Steam engine invented	
1798		Jenner starts vaccination project.
1818	Discovery of fermentation properties of yeasts	
1833	First enzyme identified: diastase by Payen and Persoz	

Date	Some important developments in science and technology	Some important developments in biotechnology
1839	Schleiden and Schwann formulate the cell theory	
1848		Public Health Act (UK)
1850		*Liebig* company founded
1855	Discovery of *Bacillus coli* (*Escherichia coli*) by Escherich	
1859	Theory of evolution: Darwin and Wallace	
1863	Pasteur invents pasteurisation	
1865	Mendel's laws of inheritance	
1868		Cholera eradicated from UK
1876	Germ theory of disease (Koch); fermentations are caused by living micro-organisms (Pasteur)	
1876	Koch discovers the anthrax bacillus Pasteur recognises principle of antibiosis	Observation of micro-organisms in beer fermentation
1881		Microbial production of lactic acid begins
1883	Weissmann: chromosomes are bearers of heredity	
1886	Koch isolates cholera bacteria	
1889	Beyerinck: "Everything is everywhere; the environment selects."	
1890		First use of alcohol as fuel
1897	Buchner demonstrates acellular fermentation, i.e. enzymes	
1902	Ehrlich and Hata develop 'Salvarsan' to cure syphilis	
1910		Sewage purification systems based on microbial activity introduced (UK)
1910 - 1920	Morgan begins to work on the genetics of the drosophila; genes are on the chromosome	
1912	Bragg (father and son) develop X-ray crystallography (technique for determination of the spatial structure of proteins)	
1912 - 1914		Röhm patents an enzyme preparation for washing Production of acetone and butanol by micro-organims (Weizmann process)

Date	Some important developments in science and technology	Some important developments in biotechnology
1916		Enzyme immobilisation used
1918		Agricultural University, Wageningen (Netherlands) founded; beginning of scientific approach to agriculture Guorui establishes a company selling digesters to produce methane (China and India)
1921 - 1922	Banting, Best and MacLeod discover insulin	
1928	Fleming discovers penicillin	
1936		Citric acid produced by fermentation
1938		Florey and Chain begin work on penicillin
1940		Isolation of cortisone Yeast grown on bisulphite liquor for human food (Germany); 15000 t/year by end of WW2
1941	'One gene, one enzyme' concept: Beadle and Tatum Discovery of streptomycin by Waksman	Cultivation of micro-organisms on hydro-carbons synthesised from coal (Germany) Demonstration of therapeutic properties of penicillin by Florey and Chain
1944		Industrial production of penicillin begins in USA Secret production of penicillin ('Bacinol') in Delft (The Netherlands) by *Gist-Brocades*
1944	Avery, McLeod and McCarty prove that DNA is the genetic material	
1945	Animal cells cultured in the laboratory	Production of yeasts on material from sugar cane in Jamaica.
1950		Increase in interest in methane from digesters (India and China) Industrial production of new antibiotics, *e.g.* streptomycin, cephalosporin
1953	Watson and Crick postulate the double helix structure of DNA	Fungal amylase used to produce specific types of syrups which could not be produced by conventional acid hydrolysis.
1955	First primary structure of a protein determined: insulin	Hoerberger concludes that current knowledge could not sustain hope of a commercially viable process for growing micro-organisms on oil Antibiotic production in most industrialised countries
1956	Discovery of DNA polymerase I by Kornberg Discovery of tRNA	Pasveer develops the continuous oxidation ditch for treating sewage

Date	Some important developments in science and technology	Some important developments in biotechnology
1957	Discovery of interferon by Isaacs and Lindeman	Fungal amylase used to produce specific types of syrups that contain a range of sugars which could not be produced by conventional acid hydrolysis Work begun in France in collaboration with *BP* for growing micro-organisms on oil
1960	Discovery of mRNA	Researchers at *Du Pont* identify active cell-free extracts of a bacterium that could 'fix' nitrogen into ammonia Increase in range of commercial products by fermentation, *e.g.* lactic acid, citric acid, acetone, butanol
1961	Nirenberg cracks the genetic code	Project begun to grow micro-organisms for human food (*Quorn*, a mycoprotein) at Lord Rank Research Centre (UK) Alkaline protease developed for washing powders by *Novo* (Denmark)
1962	Jacob and Monod postulate the operon model	*BP* builds a factory in Lavéra (France) for growing micro-organisms on oil (*Toprina*) Microbial extraction of uranium
1964	Nirenberg and Ochoa establish the genetic code (the correspondence between triplets of the bases on the mRNA and an amino-acid).	*ICI*, *Shell* and *Hoechst* plan commercial production of single cell protein (SCP) Amyloglucosidase used for conversion of starch to glucose
1967	Spatial structure of the protein lysozyme determined	
1968	Isolation of a gene by hybridisation technique	Chibata immobilised *L-amino acylase* for industrial production of amino acids
1970	Discovery of the restriction enzymes by Arber, Smith and Nathan) Discovery of reverse transcriptase by Temin, Mitzutani and Baltimore	Allergic reactions to washing powders thought to be caused by enzymes; leads to fall in use of biological washing powders
1972 - 3	Demonstration of genetic engineering e experiments : cutting and ligation of DNA molecules using restriction enzymes and ligase by Berg, Cohen, Chang and Boyer	Industrial production of wider range of enzymes for washing powders
1973	Creation of hybridomas for producing monoclonal antibodies	Ethanol production programme by fermentation for gasohol in Brazil Heat stable amylase developed by *Novo* (Denmark)
1974	Berg proposes a moratorium on biotechnology	Introduction of dust-free enzyme preparations in washing powders Increase in world oil prices begins

Date	Some important developments in science and technology	Some important developments in biotechnology
1975	Asilomar Conference calls for moratorium on practical work on genetic engineering	Monoclonal antibodies (MCABs) produced by cell fusion by **Köhler** and **Milstein** Launch of 'Microbial Resources Centres' (MIRCENS) by UNESCO and UN Enzymic production of high fructose corn syrup from glucose as alternative sweetener to sucrose by *Novo* (Denmark)
1976		*Genentech* company founded in US
1977	cDNA of insulin, the rat Growth Hormone (GH) and Human Chorionic Gonadotrophin (HCG) isolated Sequencing techniques for genes introduced by **Maxam**, **Gilbert** and **Sanger**	
1978	Directed mutagenesis introduced	'Test tube' baby (UK)
1979	Cloning and expression of the human hormone insulin and cloning of the human growth hormone in *E. coli* by **Goeddel** at *Genentech*	
1980	Genetic engineering of plant cells by **Van Montaigu** Discovery of the polymerase chain reaction (PCR) by **Mullis** at *Cetus*, a US company	Factory construction starts for industrial production of 'human insulin' made using genetic engineering
1981	Transgenic animal made by **Brinster** and **Palmiter**	US High Court rules that genetically engineered microorganisms can be patented
1982		Human insulin (*Humulin*) produced by genetic engineering on sale
1983	Acquired immunodeficiency syndrome (AIDS) described	Comité National d'Ethique established in France Test for *Chlamydia* using monoclonal antibodies
1984	Genomic sequence of the human immunodeficiency virus (HIV) determined at *Chiron*, a US company	
1985	Genetic fingerprinting invented by **Jeffreys**	
1986		Human growth hormone produced by genetic engineering on sale
1987	Beginning of the human genome project (HUGO) for sequencing the human genome	Genetically modified tobacco plants
1988		Transgenic mouse patented in US Gene for Duchenne muscular dystrophy isolated

Date	Some important developments in science and technology	Some important developments in biotechnology
1989		Use of gene therapy for treatment of genetic disorders postulated Gene for cystic fibrosis isolated
1990		Gene therapy used for treating a case of ADA deficiency Transgenic sheep 'Tracey' born
1991		24 MIRCENS now in operation
1995		Genetically modified soy bean and tomato on sale
1996		Genetically modified oil rape seed on sale

Activities for students

1. Make a list of different areas of biotechnology, *e.g.* agriculture, medicine, *etc.* and allocate some of the developments in biotechnology listed in the third column to an appropriate area of biotechnology

2. For some of the important developments in science and technology listed in the second column, indicate which developments in biotechnology (third column) depended upon them.

3. Add to the table other events and developments from the past and present when you read or learn about them from books, magazines, newspapers, *etc.*, or the Internet

4. Add to the table with information on new developments in biotechnology when you read about them or discover information on the Internet (*see page 32*).

Biotechnology on the Internet

llustrations of an application of information technology for keeping up-to-date with current and future developments in biotechnology. *NB: Although the sites listed have been checked and are known to have been working, configuration and addresses are liable to change very quickly and may not still be accessible.*

Biotechnology companies

Genentech	www.genentech.com
Clonentech	www.clontech
Monsanto (USA)	www.monsanto.com
Monsanto (UK)	www.monsanto.co.uk
Novartis	www.novartis.com
Gist Brocades	www.gist-brocades.com
Novo	www.novo.dk
Zeneca	www.zeneca.com
Hoechst:	www.hoechst.com

Research Organisations

Biotechnology and Biological Sciences Research Council	www.bbsrc.ac.uk
Medical Research Council	www.mrc.ac.uk
Wellcome Trust	www.wellcome.ac.uk
Institute of Food Research	www.ifrn.bbsrc.ac.uk

Others

European Food Information Council	www.eufic.org
Nature	www.nature.com
Science	www.sciencemag.org
New Scientist	newscientist.com
National Centre for Biotechnology Education	www.rdg.ac.uk / NCBE

(this site has comprehensive lists of up to date links to world wide biotechnology sites)

Saccaromicio and the invisible workers

Cartoons *(see the following pages)*

The bread yeast *Saccharomyces cerevisiae* is depicted as 'Saccaromicio', a fictional expert who tells the story of the considerable changes that bread making has undergone over the course of centuries. In the ancient times of the Sumerians, Babylonians and Assyrians and for centuries afterwards, the leavening of dough was attributed to mysterious phenomena and, therefore, connected with magic and religion. It was not until the 19th century that yeast was recognized as being responsible for fermentation and, therefore, having a role in the bread-making process. Today, biotechnologists are able to intervene in various ways, such as by altering the structure of the dough and modifying the traditional strains of bakers yeast, to obtain a range of improved products to suit the needs of manufacturers, retailers and consumers.