



HISTORY OF HEALTHCARE BIOTECHNOLOGY

Milestones of discovery leading to concrete benefits for society

30 years to understand DNA and develop biotech tools

Much of the excitement in modern biotechnology over the past 20 years or so has been associated with scientists' increasing ability to understand and control the basic processes of biology. The major milestones in basic research, which have resulted in an explosion of targeted research into molecular biology and genetics, have, in turn, paved the way for the biotechnology revolution. Key milestones were:

- 1943 – DNA is shown to be the basic genetic material
- 1953 – Watson and Crick identify DNA's structure as the double helix
- 1966 – DNA's complete genetic code deciphered

The history of modern biopharmaceuticals started with the discovery and manufacture of **penicillin**. Since then, the focus of the majority of biotechnological research has been in the field of pharmaceuticals.

Biotechnology offers scientists the opportunity to use the body's own molecules as medicines. As a concrete example of this, the majority of biopharmaceuticals marketed to date are recombinant therapeutic protein drugs. The advent of these new tools in the fight against disease started in the early 1970s.

The 1970s: First recombinant molecules

In **1972** Paul Berg identified and isolated a "restriction enzyme". He used this to "cut" DNA and then to "paste" two DNA strands together to form a hybrid circular molecule. This was the first [recombinant DNA](#) molecule.

1977 brought the production of the first human protein manufactured in bacteria. For the first time, a synthetic, recombinant gene was used to clone a protein. Many consider this to be the advent of the **Age of Biotechnology**. The product was somatostatin, a human growth hormone-releasing

inhibitory factor, which is used to treat people with acromegaly (as well as neuroendocrine tumours and in the intensive care of gastroenterology). Referred as "gigantism" in childhood, acromegaly is caused by an excess of growth hormone excess in adulthood and arises from growth hormone-secreting pituitary adenomas. In 95% of cases, this severe disorder is caused by a growth and often diagnosed late. Morbidity and mortality rates are high because of the associated cardiovascular, cerebrovascular and respiratory disorders and malignancies.

Currently, recombinant DNA molecules are used to relieve patients suffering from many conditions, including:

Various cancers (Cytokines, interferons & interleukins, monoclonal antibodies)

Heart attacks, strokes, Cystic Fibrosis,

Gaucher's disease (Enzymes)

Diabetes, anaemia, growth failure in children (Hormones)

Haemophilia (Clotting factors)

Hepatitis B, childhood diseases (Vaccines)

The 1980s: biopharmaceuticals are developed and marketed...

The 1980s saw intensification of research as well as the widespread marketing of the first recombinant molecules. These have the advantage of being safer and available in greater quantities than those traditionally derived from human or animal organs and tissues.

- 1978: Laboratory production of human recombinant insulin
- 1979: Recombinant human growth hormone
- 1981: Recombinant interferon gamma
- 1982: First marketing authorization for genetically engineered human insulin
- 1986: License for the first recombinant vaccine for hepatitis
- 1987: Marketing authorization for rt-PA (recombinant tissue plasminogen activator) to treat heart attacks and for a recombinant hepatitis B vaccine
- 1988: License for two anti-cancer drugs, Interleukin-2 and Polyethylene Glycol Modified IL-2.

Since the first recombinant medicine was marketed in 1982, more than 95 biotechnology medicines have been approved and made available to patients.

The production of recombinant DNA therapeutic proteins has radically changed the face of medicines. It has solved many problems:

- Thanks to biotech Factor VIII, we are less dependent on Factor VIII derived from human donor blood. **We can treat more patients with safer products.** For more information, please see the [EBE paper on Haemophilia](#).
- Thanks to the availability of biotechnology-derived growth hormone **we are now able to treat all who need it.** Previously, treatment was much more scarce, meaning that the medicines needed to be “rationed” to treat only those with the most critical cases. Since the availability has increased, we are able to treat all, even those less dramatic disorders that doctors tended to discount because the solution was not available.
- **Erythropoietin removes the need for blood transfusions** in kidney patients. Without this treatment, we would have faced serious shortness of treatments for many patients, because the BSE crisis and the steadily decreasing willingness in Europe to donate blood have meant that blood is becoming more scarce. Erythropoietin and other treatments, such as Factor VIII, meant that we could continue to treat in a way that would have been impossible without this biotech material.
- Recombinant insulin is not only safer for patients than that derived from animals, but it has also helped to **reduce the number of animals** – pigs and cows – needed to produce insulin. For example, if we had to get the insulin needed to treat diabetic patients from pigs and cows rather than making it, the numbers of pigs in the Netherlands alone would have to increase to 100 million from the current 13 million – clearly impossible!

...And modern diagnosis is also made possible

1980: Researchers successfully introduced a human gene – one that codes for the protein interferon – into a bacterium. Researchers invented a technique for multiplying DNA sequences in the laboratory by the [Polymerase Chain Reaction](#) (PCR). PCR has been called the most revolutionary new technique in molecular biology in the 1980s.

Treatment and prevention of diseases depend considerably on a precise diagnosis. PCR has opened up a whole new field in medical diagnostics. Any disease or disorder that is characterized by the presence of foreign or mutated DNA can be detected and diagnosed using PCR.

For example, before PCR, HIV infections could only be determined with the standard procedures 2-3 months after the exposure to the virus. During that time, the patient would not be receiving treatment and could have been unknowingly spreading the virus to others. PCR technology can amplify minute quantities of genetic material from between millions and more than billions of times within a few hours, allowing for the rapid, reliable detection of genetic markers for infectious diseases, cancer and genetic disorders. PCR-based tests give a greater insight into the progression and management of life-threatening infections such as HIV, hepatitis, *mycobacterium TB* and *chlamydiae*, amongst others.

PCR has also helped in identifying some 4,000 diseases of genetic origin, as it can also distinguish normal from mutated DNA. Thanks to PCR, we diagnose conditions such as cystic fibrosis, Duchenne muscular dystrophy, Huntington's disease and phenylketonuria.

The 1990s: gene sequencing leads to gene therapy

In the coming years, the number of genetic tests available will increase dramatically, due to the information gained from the Human Genome Project. The Human Genome Project (HGP) began in 1990. The goal was to identify the role of all 100,000 genes stored in human DNA. At the same time, the HGP began to explore and anticipate the ethical, legal and social implications that might arise once these genes were identified.

1990: The first gene therapy experiment is performed on a four-year-old girl with adenosine deaminase deficiency. The procedure involves inserting genetically altered cells into the veins of the patient. The Human Genome Project is officially initiated.

1995: A huge amount of research is underway as a result of increased genetic understanding. For example, the first bacterial genome, *Haemophilus influenzae*, was completely sequenced. The complete sequence of the hantavirus was reported. At the same time, more than 100 different potential new treatments were being tested in human trials, and, elsewhere, an additional 500 or more other potential therapies were in development. More than a dozen medicines are certified for use.

1996: Genetic maps of human beings and mice are completed

The New Millennium: *pharmacogenetics* – tailoring drugs to individual patients

Knowledge about the human genome developed in the 1980s and 1990s resulted in the development of a field known as pharmacogenetics. Pharmacogenetics studies how an individual with a given genotype (genetic make-up) might respond to a certain medicine or a treatment.

The growing understanding of the genetic reasons why some people might respond in a certain way to a medicine or treatment could help us predict the potential response of the individual patient. This could eventually mean that in future we would be able to offer the right medicine to the patient, one that we knew would work. This would cut waste and could offer new opportunities to meet the changing needs of healthcare systems and the demands placed upon them.

For the individual patient, pharmacogenetics could mean being offered the right treatment straight away. In theory, doctors would be able to use this knowledge to select the most effective and safest treatments for the patient. This, in turn, would potentially increase quality of life and quality of treatments.

More recently, the concept of “tailored medicines” has started to be examined, i.e., getting the right medicine at the right dose to the patient first time and avoiding so-called “try and see” prescribing. If successful, this would also have the potential to reduce costs of care, with resources being directed at diseases for which it is vital to prescribe the right

drug at the right dose from the outset, e.g., for metastatic breast cancer (Herceptin R, approved with an accompanying diagnostic test in 2000).

And the future...?

The potential for future healthcare possibilities has never looked so positive as we use our knowledge to develop treatments for conditions where previously no treatment existed and – potentially – cures where previously only treatments existed.

Our knowledge about the genetic make-up of people and the genetic basis for many diseases and conditions could mean that we have an ever-bigger “tool box” to treat disease.

It is important we make sure that our regulatory and healthcare frameworks are well-constructed to handle these exciting and new developments to ensure that the biotech milestones can deliver on their promises. If we can achieve this, this ongoing research potential could become a reality for patients everywhere in the form of new diagnostics, new treatments and – eventually – maybe even new cures.

EBE (European Biopharmaceutical Enterprises) aims to promote a positive scientific, economic and regulatory environment for healthcare companies involved in life science technologies within Europe. The EBE group currently comprises 37 members engaged in research in Europe involving the application of emerging bioscience technologies with the aim of launching new healthcare products.

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