Drugs and drug development: story of pharma

The birth of pharma

The emergence of the pharmaceutical industry in the 19th century revolutionised the way we access medicines

The Victorian era saw the beginnings of the pharmaceutical industry. By the end of the 19th century, medical doctors had become established pillars of society. They would diagnose illness and write prescriptions. The medicines themselves would be prepared by apothecaries – the dispensing chemists of the day. This conventional system coexisted with a flourishing trade in 'patent medicines' or quack cures.

The Victorian era saw a series of profound changes. First, the modern scientific disciplines began to emerge, and science began to move into specialist facilities such as laboratories. With the emergence of germ theory, it became clear that microbes were responsible for many of the killer diseases of the day.

Paul Ehrlich and others proposed the idea of 'magic bullets' – chemical compounds that attacked and destroyed only infectious organisms. Chemists began to purify the active principles from plants to provide a supply of drugs. The painkiller morphine was by now isolated from the opium poppy and being produced commercially. Other plant-sourced products included colchicine from the autumn crocus, a treatment for gout, and atropine from deadly nightshade, which was used by wealthy women to dilate their pupils, supposedly giving them more attractive eyes.

Making medicines

Yields were low, however. So chemists began to explore ways to make useful compounds by chemical synthesis. In the 1850s, 18-year-old prodigy William Henry Perkins tried to synthesise quinine from coal tar; instead, he produced the first synthetic dye, mauvein (mauve). This colour, associated with royalty and privilege, was difficult to obtain by natural means and highly prized. Perkins made a fortune and also helped create a successful synthetic dye industry, which Germany came to dominate.

In a neat twist of fate, the chemicals produced by the dye industry turned out to have medically useful properties, leading to the appearance of many famous pharmaceutical company names, including Hoechst, Bayer, Sandoz and Ciba.

Further reading:

Victorian medicine: from fluke to theory

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Paul Ehrlich: Biographical

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The chemical history of morphine: an 8,000-year journey, from resin to de-novo synthesis

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Atropine

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Pharma's post-war expansion

In the past 75 years, the pharmaceutical industry has become a huge global enterprise

After World War II, drug companies led a therapeutic revolution. Key discoveries of the early 20th century – notably insulin, vitamins and antibiotics – were mass manufactured and available to all.

New compounds were ushered in: cortisone for inflammation, drugs to treat heart conditions, antibiotics to cure syphilis and tuberculosis, and psychiatric drugs to treat (rather than lock up) the mentally ill.

Yet the ‘white heat of technology’ that inspired the 1960s has given way to a more sceptical mood, and pharmaceuticals are no exception. The drugs had side-effects or were addictive. Bacteria developed resistance. Progress in tackling some diseases has been disappointingly slow. Doctors are accused of dispensing medicines with little thought for patients’ greater wellbeing.

At the same time, concerns have grown about the tactics of pharmaceutical companies – their marketing muscle, their political influence, their activities in low-income countries and their alleged manipulation of clinical trial data to support their own products.

Pharma is said to be more profitable than any other business. In 2018, global spending on prescription drugs reached US$1.2 trillion (£0.96 trillion), and it is estimated that this figure will exceed $1.5 trillion (£1.2 trillion) by 2023.

Are such sums excessive? Drug discovery is a risky and expensive business and, in return, pharmaceutical companies provide life-saving medicines. But some people have voiced concerns over how the industry operates. They accuse drug companies of spending huge sums promoting their products directly to doctors and lobbying politicians.

In 2018, according to the Pharmaceutical Research & Manufacturers of America, its members, include Johnson and Johnson, Merck, Pfizer and Sanofi, spent $27.5 million on lobbying. Independent groups claim the figure is far higher and that the industry is spending vast sums fighting plans to limit price increases and profits on drugs. Meanwhile, in the UK, the British Medical Journal revealed that the National Health Service (NHS) bodies responsible for planning healthcare received thousands of payments from drug companies that were not publicly disclosed.

Medicines from natural products

Nature has proved a lucrative source for many drugs

From deep-sea vents to the plant-choked jungles of Brazil and Malaysia, scientists are scouring the globe in search of the next natural product to cure some of our most intractable ills. Nature is a treasure trove of useful chemicals, and today’s pharmaceutical companies are hunting for life-saving agents in animals, plants, fungi and bacteria.

Indeed, nearly half of all drugs were originally derived from natural sources. For instance, the most widely used breast cancer drug, taxol, was developed from the bark of the Pacific yew tree. An important cancer drug, vincristine, was discovered in the rosy periwinkle, native to Madagascar. Aggrastat, which inhibits blood clotting to help prevent heart attacks, is based on the venom of the saw-scaled viper from Africa.

Bioprospecting or biopiracy?

The industry has a long history of bioprospecting – hunting for natural drugs in exotic locations. One argument in favour of maintaining the Earth’s biodiversity is that medically useful products may exist in as-yet-undiscovered organisms.

A good starting point is often material already thought to have healing powers, often through its use in indigenous medicine – the extracts can be used in a purified form but pharmaceutical companies often prefer to try to isolate the active ingredients to provide a template for building synthetic drugs. As indigenous people may not benefit from the commercial development of pharmaceutical products, some use the term ‘biopiracy’ to describe this ‘borrowing’ of native knowledge

Recently, profit-sharing schemes have been set up. Most notably, the Nagoya Protocol, which after several years of negotiations, was adopted by the Convention on Biological Diversity in 2010. It aims to ensure that fair compensation is awarded to the countries and relevant indigenous communities where genetic resources are found, not only for the use of the resource but also for their traditional knowledge.

The history of painkillers

The discoveries that launched morphine, aspirin and cannabis

For centuries, opium was the only powerful painkiller available, and probably the most important drug in a doctor's bag. The Ancient Egyptians used opium from poppy (*Papaver somniferum*) sap, to stop children crying, and the ancient Greeks prescribed it enthusiastically as a health tonic though it was known to be addictive even then.

Benedictine monks in 800 CE used it as a painkiller and mixed it with herbs to make anaesthetics. Not surprisingly, opium has been called the 'joy plant' and 'a gift from God'. Florence Nightingale, who was an invalid for much of her life, found pain relief by injecting opium.

The isolation of morphine, the active ingredient, was published in 1805. It was later marketed by Merck. Even today, opioids (chemicals related to morphine) are the mainstay of severe pain management in the terminally ill.

Opioids act on pain-processing receptors on nerve cells. These receptors are targets for naturally-occurring opioids made in the brain, but opioids hijack them to modulate pain signals. Through a series of cellular events, the binding of opioids reduces the release of neurotransmitters, the chemicals that pass a nerve impulse from cell to cell.

Non-steroidal anti-inflammatories (NSAIDs) Aspirin is one of today's most frequently used drugs. This extensively used painkiller has been around for thousands of years. In ancient Greece, the physician Hippocrates wrote about a bitter powder extracted from willow bark that could ease the pain of childbirth. In 1838, pharmacists isolated the active compound from the willow tree – salicylic acid – and it became a popular treatment for rheumatic pain. In 1897, Felix Hoffman at the German dye manufacturer and pharmaceutical company Bayer modified salicylic acid to produce the less toxic acetylsalicylic acid and the trade name Aspirin was coined.

Aspirin is an example of a non-steroidal anti-inflammatory drug (NSAID) – as well as being a painkiller, it reduces fever and inflammation. It has also been widely used for protecting against heart disease and stroke, although evidence for its use in this regard is inconsistent. Another common NSAID is ibuprofen. Both are sold over the counter.

NSAIDs act on a group of enzymes known as cyclooxygenases (COX), which are needed to make a range of signalling molecules. One drawback is their tendency to damage the lining of the gut. When it was discovered that the COX enzyme in the gut lining differed from that responsible for pain and inflammation, researchers rushed to develop inhibitors that did not affect the gut enzyme. These new blockbuster drugs, the COX-2 inhibitors, were widely used until 2004, when a study showed that one COX-2 drug, Vioxx, increased the risk of heart attack and stroke. The drug was withdrawn, prescriptions for other NSAIDs fell and there were many new safety studies on the drugs. Today, the Medical and Healthcare Products Regulatory Agency in the UK recommends prescribing the "lowest effective daily dose" based on an assessment of a person's individual risk factors.

Coal tar and cannabis

In the early 19th century, English industrial chemists produced a novel painkiller – phenacetin – from coal tar. This eventually led to paracetamol, which is a useful treatment for chronic pain because it can be used with other analgesics, including opioids, in low doses. It must be used with caution as high doses can damage the liver.

Cannabis (an extract from *Cannabis sativa*) can be a powerful painkiller. The Romans used it to ease pain, and its medicinal use may go back even further, to 2700 BC and the Chinese emperor Shen Nung, who used it to treat rheumatic pain, as well as malaria and constipation. In the 19th century, Queen Victoria took cannabis to ease period pains.

Although cannabis is a prohibited substance in many countries, it is now licensed for medical use in some, including Canada and most US states. In the UK, medicinal cannabis was licensed in 2018 for "special clinical need", but it is thought that fewer than 100 people were prescribed it in the first year due to the

requirement that it be prescribed by “specialist doctors”. People with multiple sclerosis (MS) say cannabis reduces muscle spasms, pain and tremors. Clinical trials to test the medical effects of cannabis’s main active ingredient – tetrahydrocannabinol – have shown that it does not slow the progression of the disease. However, medical advisers at the MS Society say that about 1 in 10 people with MS could benefit from cannabis treatment for pain and spasms, when other treatments do not work.

Some people with MS say the medicinal form of THC does not provide the same pain relief as smoking cannabis, whereas medical advisers argue smoking it is harmful to health. Growing evidence that cannabis consumption increases the risk of psychosis is likely to limit its use over the medicinal THC alternative.

Despite these substances, pain – particularly chronic pain – is common and difficult to treat. The hunt for compounds that lessen pain continues.

Further reading:

The chemical history of morphine: an 8,000-year journey, from resin to de-novo synthesis

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Dwale: an anaesthetic from Old England

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The life of Florence Nightingale

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The rise and fall of aspirin in the primary prevention of cardiovascular disease

https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(19)30541-0/fulltext

The aspirin story – from willow to wonder drug

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Non-steroidal anti-inflammatory drugs

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Paracetamol

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The placebo effect

Does a medicine depend only on the active ingredients within it?

Oddly, the answer is no. No matter what is in them, painkilling medicines are more effective when wrapped up in ‘proper’ pharmaceutical packaging. Red, yellow or orange pills provoke a strong stimulatory or antidepressant effect; blue, purple or green tablets are good for tranquillising reactions.

In 1955, anaesthesiologist Henry Beecher tried to quantify the placebo effect. He found that an average of 35 per cent of 1,082 patients with different types of pain across 15 studies got satisfactory relief from a placebo. Remarkably, then, more than one in three patients improved even though they were not receiving a medicine.

What might be going on? In reality, there are likely to be several ‘placebo effects’. For example, disease may spontaneously regress in some cases.

But there is growing evidence of physiological changes linked to the placebo effect. Brain imaging studies, for example, show differences in brain areas associated with pain when people are anticipating pain relief (even if it never actually arrives).

Recent studies suggest placebo effects may work via the nerve pathways mediated by dopamine, opioid and cannabinoid receptors. Changes in the immune system and cardiovascular function have also been linked to placebo responses. It therefore appears that expectation can influence physiology and that mind over matter is a real phenomenon.

The placebo effect may lie at the heart of complementary medicine, in therapies such as homeopathy and acupuncture. Although these therapies may perform no better than placebos in clinical trials, the placebo effect itself is often better than nothing. However, the evidence base for many complementary therapies is not recognised by the majority of scientists and they are not considered an option for serious conditions or when effective medicines are available.

There have been suggestions that doctors should deliberately use the placebo effect for tricky patients – giving them a dummy medicine that they know won't work but the patient believes will. Many doctors will admit privately to doing this. But it does raise issues about trust, as doctors have to deliberately deceive patients to help them get better.

However, placebos have even shown to be effective in cases where patients know they are getting a placebo. In one US study, patients with irritable bowel syndrome improved on placebos even though they were told that they were being given a sugar pill. The scientists who carried out the study suggested “open label” placebos could be worth a try in clinics.

Further reading:

The power of drug colour

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The powerful placebo

https://jamanetwork.com/journals/jama/article-abstract/303530

The power of nothing

https://www.newyorker.com/magazine/2011/12/12/the-power-of-nothing

The neuroscience of placebo effects: connecting context, learning and health

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6013051/

Complementary and alternative medicine

https://www.nhs.uk/conditions/complementary-and-alternative-medicine/