

Chapter 2

Seven Tales of a Patent

The Colour Mauve

No matter how creative, intelligent and well-trained a scientist may be, serendipity and sheer luck can make a huge difference. But not everybody is able to detect the chance discovery or find an application for it. One is reminded here of Louis Pasteur's oft-quoted aphorism that 'where observation is concerned, chance favours the prepared mind', Sir Peter Medawar's that 'a good scientist is discovery-prone', or golfer Gary Player's that 'the harder you practice the luckier you get'.

In 1856, 18-year-old William Henry Perkin at the recently established Royal College of Chemistry in London was set the task of making quinine using coal tar, an industrial waste product of gas lighting that was being produced in high volumes at the time. This was in fact a futile task since the state of the chemical arts had not then reached a level that would have made it possible, feasible as it appeared to Perkin and his professor, August Wilhelm Hofmann.

Coal tar happens to be a rich source of interesting organic compounds like benzene and phenol. Starting with aniline, a coal tar derivative discovered several years earlier, Perkin produced what appeared initially to be a worthless black gunk. Many other scientists would just have thrown it away and tried again, or done something else. But curiosity was clearly part of Perkin's nature. He added methylated spirits and water, and found that the substance stained his test-tubes bright purple. After that, he lost any interest he had in cures for malaria, and turned to the possibilities of dyeing. He tested it on cloth, and realising the commercial potential, filed a patent and set up a company to manufacture and sell it. Perkin's dye was not the first aniline dye. Nor was it the most profitable of those early years.

But it was the first to be commercially successful, and its implications were far-reaching.

Although directed to quinine synthesis by Hofmann, the credit for discovering the properties of mauve and in effect establishing a completely new science-based industry rightly goes to Perkin. In any case, the task of making quinine was way beyond the means of anybody at the time. It was one thing to know the chemical formula of a molecule like quinine, which chemists at the time did; it was quite another to know its three-dimensional configuration. Indeed, so challenging was the task of synthesis that it was not to be achieved for almost another century. But ignorance and error can lead to unforeseen achievement if the timing is right. 'If Perkin had been born twenty years later, he would have known how fruitless his search would have been, and thus would not have blundered into mauve.'¹ Perkin conducted the experiments leading to the discovery of mauve in his own home and without Hofmann's oversight. Besides, Hoffman was rather underwhelmed by Perkin's discovery and felt that he should stick to doing scientific research rather than enter the risky world of commerce.²

Perkin's discovery paved the way for new coal tar-based industries to emerge rapidly and become incredibly productive in terms of the variety of products discovered and entering the market and in the extent of the wealth created. One of these industries was pharmaceuticals, but there were several others. As an eminent British scientist writing at the beginning of the twentieth century put it rather presciently:

The manufacture of synthetic medicinal agents, artificial perfumes, sweetening materials, antitoxines, nutritives, and photographic developers are all outgrowths of the coal-tar industry, and in great part still remain attached to the colour works where they originated. Of these subsidiary industries the most important is the manufacture of synthetic medicinal preparations, which has already attained to large proportions, and bids fair to revolutionise medical science.³

The synthetic dyestuff industry came to be dominated by new German chemical firms like Bayer, Hoechst,⁴ BASF,⁵ and AGFA.⁶ The first of these soon became more famous for drugs than dyes. Indeed, the modern pharmaceutical industry can be said, in part, to be an offshoot of the dyestuff industry. As for Perkin, whether or not he was a genius is a moot point. What he definitely had was initiative, curiosity, intelligence, entrepreneurial spirit, and of course good fortune. And for that we should all be grateful.

As for patenting, Perkin's invention heralded a major change. With the patenting of fine chemicals and processes to make them, new science-based industries appeared almost from nothing and these generated huge revenues. The patent stakes for such firms, whether they were innovators or imitators, were immense. Consequently, success depended often on clever use of the patent systems of their own countries *and* of their overseas markets. Their ability to be strategic about patenting (and, increasingly, trade marks) depended on what patent laws allowed them to protect, or to get away with. Consequently, the chemical industries became active lobbyists influencing as far as they could the drafting of patent laws. Where they found underprotection (as they saw it), companies would join with rivals to persuade the government to strengthen protection. Where they found overprotection, they would lobby either for less protection, or alternatively collaborate with other firms to mitigate market distortions arising from either too many patents or from the monopolies created by small numbers of overly broad patents. They would do this, for example, by pooling their patents or shifting their operations to neighbouring countries. When patents were insufficient to keep prices high for lengthy periods, companies sometimes formed price-fixing cartels. When one looks at the business practices of today's pharmaceutical and biotechnology companies, it becomes obvious that these lessons were learned from the dyemakers 130 years earlier when they were starting also to make drugs. Furthermore, governments became aware of the economic stakes involved and consequently became very interested not only in their own patent laws but in those of their perceived economic competitors. Again, this is very much the case today.

Aspirin

Aspirin, first sold in 1899, was one of the first patented and branded pharmaceutical products, and has remained an incredibly popular treatment for headaches and mild fevers ever since. There is much that is very old about aspirin and much that is also quite new. Patented and trade marked in the late nineteenth century, aspirin's natural precursor was known about for thousands of years, yet nobody knew how it worked until the 1970s. New discoveries about aspirin continue to be made.

Aspirin occasioned an incredible amount of learning in terms of marketing and intellectual property management on the basis of levels of innovation that were quite modest. One might even go so far as to suggest that it was in the marketing and intellectual property management that the real innovation could often be found, and not so much in the science. Indeed, aspirin is a prime example of how much money can be made from some fairly mundane tinkering in the lab as long as the marketing is done well. The lesson was well learned by the pharmaceutical industry.

As with mauve, there is a malaria connection. Bark of the willow tree, which contains the active principle, was at one time promoted in England as a treatment for ague, a catch-all word for various afflictions including malaria. Another connection is that Bayer, an early manufacturer of synthetic dyestuffs like mauve, is the company that patented and trade marked aspirin. As we will see, the company's patents on aspirin proved to be quite controversial, as did the identity of the true inventor.

The notion that willow bark has therapeutic qualities dates at least as far back as 5000 years BC in ancient Ur. It was also known to the ancient Egyptians. Later on, it was recommended by Hippocrates in fifth century BC Greece as an analgesic, the Roman Celsus as an anti-inflammatory agent, and the famous Claudius Galen, physician to Roman emperor Marcus Aurelius, also as an analgesic.⁷

In the modern era, scientific attention was turned towards willow bark following a discovery made in 1757 by one Rev. Edward Stone, a vicar in Chipping Norton, Oxfordshire. He sucked on a piece of willow in a marshy area near the town and noting its bitter taste, which made him think of quinine ('the Peruvian bark'), he wondered if this might be useful in treating the ague. His reasons for trying willow are not difficult to surmise given the similar source of quinine, and being guided by the long-established notion that the places where diseases are considered to originate, in this case marshy ground, tend also to be those where their cures reside. There is no evidence, though, that he was inspired by the writings of those ancient Greeks or Romans. He dried some of the bark, reduced it to a powder, and tested it on 50 fever sufferers over five years. It was particularly effective on mild fevers but offered some relief to more severe ones. He reported this to the Royal Society's journal, the *Philosophical Transactions*, which published his findings six years later, mistakenly under the name of

Edmund Stone.⁸ Stone's discovery soon piqued the interest of scientists both in England and on the continent.

The nineteenth century experienced tremendous advances in chemistry. French scientists successfully isolated phytochemicals like strychnine, caffeine, nicotine and quinine. Other chemists were learning how to synthesise natural products in the lab and to produce derived substances with no equivalent in nature. Both the 'isolators' and the 'synthesizers' contributed to the development of aspirin.

In 1828, a German scientist, Johann Buchner, isolated a crystalline form of the active compound from willow bark, naming it salicyn after *Salix*, the Latin name for willow. Others improved the method, including the Italian Raffaele Piria, who named the crystal salicylic acid.⁹

Willow is not the only source of the active principle. A Swiss pharmacist, Johann Pagenstecher, found that an extract of the meadowsweet flower, *Spirea ulmaria*, relieved toothache and rheumatism. The article he published was read by a German chemist called Karl Jacob Löwig, who conducted experiments and discovered that the extract he made from this plant was salicylic acid.

Salicyn and salicylic acid share the drawback that swallowing them in the doses necessary to be effective causes an irritating burning sensation in the stomach. In 1853, Charles Frederic Gerhardt, a chemistry professor at Montpellier University modified salicylic acid to produce a crude form of acetylsalicylic acid (ASA) that was less irritating. In 1859, Herman Kolbe of Marburg University came up with a very efficient process for making ASA from coal tar, and this formed the basis in 1874 for the first industrial scale production of the chemical, by the Heyden Chemical Company which was founded by a former student of Kolbe's, Friedrich von Heyden. Heyden's product was not a great success because it was insufficiently pure to eliminate stomach irritation, but the company came to play its part in the aspirin story 30 years later. Another form was produced by Karl Johann Kraut in 1869.

While drug extraction, purification, synthesis and production were becoming scientific activities, the sale of medicines continued to lack respectability. One reason is that in the absence of trade and production regulation, there was a plethora of so-called 'patent' remedies on the market that simply did not work, while others that may have worked were not

subjected to tests which might have differentiated them better from the useless ones and given them legitimacy.

Thomas Maclagan was a Scottish doctor who worked for several years in a Dundee hospital and then moved to London. Acquiring quantities of salicin, he conducted a controlled clinical trial and reported his positive findings concerning treatment of acute rheumatism patients in an 1876 edition of *The Lancet*.¹⁰ This article attracted the attention of doctors in France and Germany who wrote to the journal that they had obtained similarly good results from salicin and also salicylic acid. As Dormandy put it, 'if in modern times the Reverend Edward Stone was the "discoverer" of salicin as a potential drug, it was Maclagan who gave it medical standing.'¹¹ Nonetheless, the unpleasant side-effects had not been eliminated.

The story now shifts to the laboratories of Bayer. Like its competitors, Bayer had become aware from an early time that drugs that were no more than modest improvements on competing ones could sell well with an aggressive marketing and intellectual property strategy. This remains very much the case. Accordingly, whether a new drug was 'new' enough to be patentable in overseas markets (only process patents were available in Germany at the time) was not necessarily as important as a commercially attractive name that could be trade marked. German law became quite friendly to firms seeking to use trade marks in marketing. The German Trademark Law of 1894 had a powerful influence on German pharmaceutical companies. The latter's protection of trade names, packaging, and even the way companies wrote their names justified heavy investment in advertising to associate companies with health, quality, and serious research in the public mind.¹² One of Bayer's first marketing successes, for example, was its Phenacetin brand, a modified form of a coal tar-based waste product. Even old drugs could succeed if the 'right' trade name was chosen. Perhaps the first instance ever of trade mark use in the marketing of an unoriginal pharmaceutical product is Kalle's Antifebrin, a form of aniline, against which Phenacetin, a chemically similar drug, was placed on the market to compete. A significant marketing innovation was Bayer's decision to stop selling powdered ASA to wholesalers and instead make its own aspirin pills, stamping the Bayer cross logo on each one — and with it the association between aspirin and the company in the minds of each consumer.¹³ For Bayer, it was important to keep 'Aspirin' the Bayer-owned

brand from becoming ‘aspirin’ the generic product associated with no particular company. As it turned out, war was the biggest threat to the success of this strategy.

But Bayer was not just about clever marketing and intellectual property policy. The company was well aware of the value of recruiting good scientists and doing its own research and development. Carl Duisberg, hired as an ambitious young scientist, is a key figure here. He was largely responsible for turning Bayer into a research-based company with sophisticated marketing strategies. For doing so, he is probably the most important person in the long history of the company next to its founders. He also had a major influence on the modern pharmaceutical industry and, as even, as we will see, on the evolution of European patent law.

In fact, around this time, Bayer was following up on two competing possibilities. One was diacetylmorphine, discovered originally by a scientist at St Mary’s Hospital in London, where Alexander Fleming worked some decades later.¹⁴ Bayer had hoped to market it under the name ‘Heroin’. The other was acetylsalicylic acid. While Duisberg and his head of pharmacology, Heinrich Dreser favoured heroin, two Bayer chemists, Arthur Eichengrün, who was head of pharmaceuticals, and Felix Hoffman, took matters into their own hands and arranged for a trial of their modified form of ASA. The trial was a great success with none of the usual side-effects. Duisberg and Dreser were far from happy that the two of them had gone behind their backs. Nonetheless, the commercial possibilities were undeniable. Before marketing, a name had to be chosen for the product. It was apparently Eichengrün’s suggestion that it be named aspirin after acetyl, the Latin name for meadowsweet (*Spirea*) and the added suffix ‘-in’, which had become common at the time in drug names.

Hoffman, Eichengrün and Dreser are all associated with the 1897 ‘discovery’ of aspirin, though there is some controversy as to who played the most important role. Recent research suggests that Eichengrün’s contribution was deliberately understated in the 1930s, presumably because he was Jewish, and is still not properly acknowledged even by the company.¹⁵ Whatever the case, while these three came up with the specific form of ASA that became aspirin, several other people played their parts. Indeed, aspirin evidences how the last piece in the innovation ‘jigsaw’ puzzle is often a rather tiny one compared to the size of some of the pieces put in earlier.

What the three scientists most closely involved achieved was really rather modest, important as it nonetheless was. Piria, Maclagan and Gerhardt are obviously key people, but there were other contributors going all the way back to Edward Stone, who arguably was the one indispensable actor in the whole story. But as far as aspirin the product is concerned, credit must really go to Carl Duisberg and Bayer who pioneered the modern science-based corporation able to generate innovations, albeit mostly incremental, on a vast scale and market them with skill, aggression and clever intellectual property strategy.

But was there an invention at all? ASA was of course a known substance and Heyden had been selling it for some years. Patents were filed in Germany, the United States and Great Britain. The German application was accepted at first but was then rejected because only processes were patentable at the time and not chemicals themselves, and also because it was not new anyway. The British patent was filed in 1898 but was invalidated in a 1905 infringement case. The court accepted the defence of *Chemische Fabrik Von Heyden*, which had been marketing a very close equivalent to aspirin since 1901, that it lacked novelty. The US patent, on the other hand, which was filed in 1900 and named Hoffman as the inventor managed to survive a 1909 infringement case.

The aspirin story does not end there. It is as long as the pharmaceutical industry itself — one reason why it is such a fascinating and illuminating one. And it is still not over. Due to the First World War, Bayer lost control of its Aspirin trade mark in various countries, including the USA and the UK. During the inter-war years, an increasing number of rival products became available. These included Aspro, another ASA product developed in Australia and sold by Nicholas Proprietary, and others that contained mixtures of aspirin with other ingredients.¹⁶

Just after the Second World War, Reckitt and Colman's soluble aspirin called Disprin came on the market. There was also Anacin (or Anadin), Bufferin and Excedrin. All of these were marketed aggressively and at times successfully. Interestingly, three old compounds gave rise many decades later to a revolution of sorts in the market filled by these products. The first of these was acetaminophen, synthesised by Bayer in 1878 but rejected on toxicity grounds. The second and third were Antifebrin (acetanilide) and Phenacetin (acetophenetidine). In the late 1940s, scientists at Yale

and New York Universities discovered, first, that acetanilide was converted in the body into acetaminophen, and second, that acetophenetidine was similarly transformed into acetaminophen. The substance seemed to be completely safe, suggesting that Bayer might have been testing contaminated samples all those decades earlier. In the 1950s it was marketed in the UK (but not the US) as Panadol, and like Aspro and Disprin, was a great success. When it became an over-the-counter product, it was given the generic name paracetamol. Sterling, which had acquired Bayer Aspirin in the United States, chose not to market Panadol in the US as it would have competed with its aspirin branded product. But an acetaminophen equivalent to paracetamol came on the market anyway in the late 1950s. This was McNeil Laboratories' Tylenol, which soon fell into the hands of Johnson and Johnson when it took over the company. Perhaps the last great rival to aspirin is a product discovered by Boots in the UK that was a genuine triumph of science. This started in the 1950s, an extraordinarily productive era for pharmaceutical discovery as it happens, as an attempt to produce an anti-inflammatory alternative to replace cortisone, which had numerous side-effects (see Chapter 5). Mindful of the anti-inflammatory properties of aspirin, Boots's Stewart Adams and John Nicholson looked far and wide for chemical types that produced effects like aspirin without being chemically related. In the early 1960s, after years of effort, they came across the phenylpropionic acids, and found a number of compounds whose analgesic, anti-pyretic and anti-inflammatory powers were far superior to aspirin. A patent was filed in 1962 claiming various related chemicals. A number of these fell by the wayside, including one that was briefly marketed but then withdrawn. Seven years later, the best of these came on the market under the name of Brufen. It is now known to millions of people by its generic name of ibuprofen or in the United States as Advil which has been available as an over-the-counter branded generic product since 1984.¹⁷

During all this time, aspirin's mode of action was unknown. It remained that way until 1971, when it was discovered by John Vane, a pharmacologist at the Royal College of Surgeons who won a Nobel Prize for this achievement. Vane had become interested in a class of fatty acids called prostaglandins which perform a variety of functions and are produced in the body from another chemical found in cell tissue, arachidonic acid.

One weekend in April 1971, it struck him that aspirin and related drugs known nowadays as the non-steroidal anti-inflammatory drugs (NSAIDs), which include all the ones mentioned in this part of the chapter, worked by inhibiting the biosynthesis of prostaglandins from arachidonic acid. This would account for the therapeutic effects of aspirin, which are to reduce fever, pain and inflammation, as well as for the two main side-effects: stomach pain caused by weakening of the stomach lining, and thinning of the blood due to interference with anti-platelet activity. Both result from absence of the right prostaglandin caused by aspirin.¹⁸

Subsequent research showed that the prostaglandin manufacture process requires the intervention of an enzyme called cyclo-oxygenase (COX), which is especially important as it is also involved in converting one type of prostaglandin to another. COX comes in two forms and the way that different NSAIDs work depends on the dose and on whether the drug in question is more or less active against COX-1 as compared to COX-2. The COX-1 enzyme is involved in the making of prostaglandins concerned with the gastro-intestinal tract, while COX-2 assists in the synthesis of prostaglandins relating to inflammation and pain.

Vane suggested that understanding aspirin's mode of action could well lead to further medical applications. Since then, it has turned out to have other therapeutic applications, especially in preventing heart attacks and strokes, though several other uses seem to be feasible too. Indeed, aspirin also instances how new uses of a drug may continue to be discovered as scientists learn more about the chemical, the ways the chemical interacts with the cellular machinery of humans (or infective agents of humans such as bacteria) and about human biology and the diseases that afflict us. As we will see later on, the fact that revisiting old drugs in this way can lead to commercially interesting new discoveries explains the increased availability nowadays of patents for new uses of old things. Indeed, patents relating to aspirin and other NSAIDs continue to be filed.

Warfarin

The warfarin story is a fascinating one showing how observations of natural phenomena unrelated apparently to human health may eventually lead

to an important new pharmaceutical product. It also confirms that the difference between a drug and a poison is often not so different from the one between a flower and a weed. It largely depends on whether it's in the right place or the wrong place, and whether there's the right amount or too much.

Warfarin is a university invention named after the Wisconsin Alumni Research Foundation, which owned the patents and licensed them to industry. The pathway to warfarin's discovery began with investigations undertaken to find out why cattle in North Dakota, USA, and Alberta, Canada, in the 1920s were suffering severe internal haemorrhages from diminished ability of the blood to clot. This was linked to their consumption of stored sweet clover hay. While often fatal, the hay did not cause permanent bodily harm in that full recovery from 'sweet clover disease' was often attained when the afflicted livestock were given blood transfusions and simply not fed the spoiled clover. By 1931, it was known that the loss of coagulability was linked to a reduced activity or presence of prothrombin, one of the substances involved in blood clotting.

Karl Paul Link, a biochemist at University of Wisconsin, started work on this topic in 1933. One afternoon in February of that year he was visited by a Wisconsin farmer called Ed Carlson, who had travelled for 190 miles through a blizzard, according to Link's own account, with 'a dead heifer, a milk can containing blood completely destitute of clotting capacity, and about 100 pounds of spoiled sweet clover — the only hay he had to feed his cattle.'¹⁹ Extracting and purifying the haemorrhagic agent was a six-year effort involving Link and several of his colleagues and PhD students including Harold Campbell, Charles Huebner and Mark Stahmann. 'Finally in the dimness of dawn on June 28, 1939, after working all night, Campbell saw on a microscope slide what turned out to be crystalline Dicumarol. Two hours later he had collected about 6.0 mg. of it.'²⁰ This achievement was followed by the isolation of 1,800 mg. by Stahmann with Miyoshi Ikawa, after which Huebner determined the substance's chemical structure as 3,3'-methylene-bis (4-hydroxy-coumarin). In April 1940, Huebner synthesised it.

The substance was marketed for human therapeutic use under the name Dicumarol, but it was generally considered as being not very safe, albeit still useful, largely due to initial unwillingness to accept the finding of

Link's team that vitamin K, which in the human body is involved in prothrombin manufacture and is chemically related to Dicumarol,²¹ is an effective antidote in cases of excessive bleeding by patients taking the drug. By 1942, Link's team had synthesised over 100 related chemicals, and these were waiting to be tested. While recuperating from illness in late 1945 and early 1946, Link did some reading on rodent control. In his entertaining account, Link prepares us for what came next:

Now brace yourselves, for I propose to shift from a 'cow poison' that had become a drug of substantial clinical usefulness, to a 'rat poison' converted to a drug, which has I believe most of the desirable features that can be expected from an anticoagulant to be given primarily via the oral route.²²

Two convenient-to-make derivatives showed powerful and uniform activity in rats and dogs. One of these, numbered 42, came on the market in 1948 as a rat-killer, and turned out to be a hugely successful product. It was named warfarin by Link after the Wisconsin Alumni Research Foundation (WARF) with the added 'arin' from coumarin, the natural product from which it was derived.

There the story might have ended. Link believed that warfarin should be tried out on humans, but clinicians were understandably sceptical that a powerful rodenticide could be either safe or effective as a treatment for humans. Link may never have got the chance to test out his theory if it had not been for his learning in April 1951 of an army conscript who had attempted suicide with warfarin. Link describes what happened:

The inductee had followed the multiple dose directions on the package. It became clear to him that warfarin was not an efficient agent 'to shuffle off' this 'mortal coil.' It allowed too much time for thinking — so he went to the hospital with a fully developed case of hemorrhagic 'sweet clover disease.' He was treated per the directions — blood transfusion and large doses of Vitamin K — and made an uneventful recovery.²³

The outcome was a potent, fast acting and easy to deliver anticoagulant product, warfarin sodium, marketed as Coumadin, which gained prestige when it was given to a sick President Eisenhower in 1955. It is still commonly used today. Such are the long and winding roads that drug discovery processes sometimes follow. While several people were involved in different parts of the story, Karl Link was by far the most important actor, seeing the

discovery process to its conclusion from a cow disease to a rat poison, and finally to an important pharmaceutical product. Unsurprisingly, his name is on all of the key patents relating to Dicumarol and warfarin.²⁴

Streptomycin

Streptomycin was discovered in 1943. This was the second antibiotic after penicillin. It was an incredibly significant discovery since unlike penicillin it was effective against tuberculosis. In 1948, two US patents relating to streptomycin were granted. The earlier patent that was filed covered methods of extraction and production. Filed in February 1945, it was granted in September 1948. The inventors were Selman Waksman of Rutgers University and his student Albert Schatz, who assigned it to the Rutgers Research and Endowment Foundation even though the work was financially supported by Merck.²⁵ The second patent to be filed, in August 1945, was granted two months earlier than the first one.²⁶ The inventor was Merck's Robert Peck. This one, obviously a later invention, covered not just various processes but also several crystalline salts of the streptomycin itself. Although streptomycin was a natural product that could hardly have been invented by any of the three scientists, the patent claimed to the satisfaction of the examiner that 'for the first time, streptomycin is available in a form which not only has valuable therapeutic properties but also can be produced, distributed, and administered in a practicable way'.

The discovery of streptomycin and its activity against TB was achieved by a team of scientists led by Waksman with collaborators from the Mayo Clinic who suggested to Waksman that he tested the substance against the tubercule bacilli, and later on carried out the animal tests and human clinical trials.²⁷ While Waksman received most of the credit including a Nobel Prize, as with penicillin industry was largely responsible for finding how best to mass-produce it. As for which person was responsible for the discovery, Albert Schatz claimed that he deserved a bigger share of the credit on the basis that he was the one who actually isolated the chemical in 1943, in fact just four months after Waksman had taken him on.²⁸ This issue has become quite controversial, with both individuals having their advocates.²⁹ While it would certainly go too far to suggest that Schatz was merely a laboratory drone obeying orders from above, Kingston's very

well-researched article that supports Waksman is pretty persuasive. One telling point he makes is that

To claim that Waksman took credit properly due to Schatz is to fail to understand that once pharmaceutical research had become primarily a matter of largescale, routine testing, little individual creativity was left in this work. Credit for any successful results must therefore be given to whoever is the originator or director of a particular programme.³⁰

Waksman was of course a highly experienced microbiologist and whether or not he was the one who provided the final piece in the jigsaw, he knew where to look and had gone pretty far in terms of narrowing down the search. Echoing Pasteur's famous aphorism which began this chapter, Kingston makes the following remarks:

Schatz owed the preparation of his mind for observing what might emerge in the course of this research, to Waksman. The funding from Merck that supported Schatz's work was only available because of Waksman's previous efforts and reputation — and the 'near misses' of earlier students of his, like Dubos. It was because of Waksman's collection of samples and his direction that there was a screening programme at all for Schatz to work on. It was Schatz's good luck that it was he, and not another member of Waksman's team, who was given the source of the active strain of streptomycin among those it was his task to isolate.³¹

Tagamet, Zantac and Losec

Nowadays, pharmaceutical companies are dependent for their own well-being on the success of so-called blockbuster drugs. These are the ones that bring in revenues of at least \$1 billion a year and in some cases, such as Lipitor and Plavix, considerably more than that. Obviously, patents on such moneyspinners are extremely valuable to a company, which can suffer severe profit losses when they expire. Our fifth story is really three short tales in one of three inventions from the 1970s, all of which have been world number one bestsellers: the anti-ulcerant drugs cimetidine (marketed as Tagamet), ranitidine (Zantac) and omeprazole (Losec or Prilosec). Two are closely related chemically, being so-called histamine H₂ receptor antagonists, of which cimetidine was the pioneer. Yet both were patentable. The other, Losec, was a close competitor but of a different type, known technically as a proton pump inhibitor after its mode of action. The story

shows the pharmaceutical industry at its best — applying brilliant science to develop products of great benefit to patients — and also at its worst.

These drugs testified above all to the massive profits to be gained from marrying hard-nosed business strategy to good science. Concerning the latter, while most of the drugs discussed so far relied a great deal on serendipity and trial and error with very little actual design or even knowledge of how they worked, these drugs were quite different. Cimetidine was an early triumph of so-called rational drug design in which the drug was specifically tailored to perform a highly specific task in the human body, an idea originally envisioned by Paul Ehrlich. He was a German scientist who around the turn of the century had been fascinated by the effects of synthetic dyes on human tissue and the interactions between chemicals and cells, and who famously coined the term ‘magic bullets’ for the finely targeted drugs he aimed to discover. The research leading to cimetidine and its discovery has been recognised by the American Chemical Society and the Royal Chemistry Society as a momentous achievement. As the American Chemical Society expressed it on its webpage:

The research program leading to cimetidine ... represented a revolution in the way pharmaceuticals are developed. Traditionally, the development of a new drug would often depend on the fortuitous discovery of a plant or microbial extract that showed some of the required biological activity. Using that first extract as a lead, many similar compounds would be made and tested for pharmacological effectiveness. In many cases, the researchers did not know how the drug worked, so finding an optimal compound was difficult. The development of cimetidine was radically different: it was one of the first drugs to be designed logically from first principles... Using a step by step analysis of structural and physical properties, the team made a series of histamine-based molecules, which were then tested for antagonist activity using carefully designed pharmacological assays. Today, this approach of rational drug design underpins the discovery programs of many major pharmaceutical companies.

In brief, the problem facing a research team led by James Black working at Smith Kline & French Research Institute in the UK during the 1960s and 70s was that of how to prevent the secretion of acid caused by histamines reacting with the stomach. Up to that time, ulceration caused by these secretions was difficult to prevent and surgery was often necessary. It was known that the antihistamines, which inhibited the effects of histamines elsewhere in the body, could not do so in the stomach.³² This suggested

that the histamines were blocking a different receptor in the stomach's parietal cells to the receptor type that they blocked in other parts of the body which the antihistamines targeted.³³ The known receptor type was referred to as H in a 1966 journal article that postulated the existence of the second type.³⁴ The task then became that of identifying a chemical — a competitive antagonist in the language of pharmacology — that would successfully compete with histamines for this second receptor (labelled H₂) and reduce acid production. In 1972 they came up with cimetidine, the first of an entirely new class of drugs, which became available to patients in 1976.

Unlike the practices of some companies, the researchers were allowed to publish their findings as they went.³⁵ No doubt, this alerted competitors to the possibilities, and as soon as 1978, Glaxo had come up with a more powerful H₂ receptor antagonist with fewer side-effects. For several years, ranitidine was the world's top selling drug with cimetidine as number two, and made Glaxo one of the biggest pharmaceutical companies in the world.

The Swedish company Astra, later merged with Zeneca, adopted a different approach, focusing on the mechanism by which the parietal cells produce gastric acid. It discovered omeprazole in 1979, which by its original mode of action was another class of drugs entirely, one which also had its subsequent followers.

The massive commercial success of these three drugs relied on patent protection. Cimetidine, for example, had made \$14 billion by 1994, the year its United States patent expired.³⁶ Also key was the fact that they were found to be effective against other gastric disorders than just peptic ulcers including heartburn and indigestion to name just two.

Cimetidine was unique not only in the way it was developed; it was the world's first blockbuster drug. Since it came on the market and was followed by others, companies have desperately sought such products. The anti-ulcerant drugs we looked out suggest they have sometimes done so by developing a revolutionary new class of drug as did both Smith Kline & French and Astra. However, we have also seen how they may market a similar product to an existing one that is either more effective or safer, or, and this might sound cynical, that can be marketed so well that people are persuaded that it is. Ranitidine was a genuine improvement but in other cases there are reasonable grounds for scepticism that the 'me too' is any better at all than the original.

Blockbuster drugs can only be blockbusters if they are patented and for only as long as the patents remain in force. The value of the patent system then becomes more apparent than ever as is the threat once the patents expire. Companies nowadays are obsessed with the problem of what to do once patents on blockbuster drugs expire, when generic products enter the market and the price normally drops quite dramatically. They can be very creative, and often quite devious, in their efforts to continue the effective monopoly period or else to ensure that patients continue to use their products on the basis of having better versions available. A good example is AstraZeneca's Nexium, a product that was both chemically and therapeutically virtually identical to Losec, and whose marketing presents the industry in a far less favourable light. With Losec about to go off patent, AstraZeneca sought to switch patients over to the new drug which was ten times more expensive than the former drug. They did this by deploying aggressive marketing tactics claiming that it was both newer and better. In fact, it was hardly new, and the improvement was quite modest.³⁷ This effort cost hundreds of million dollars in marketing, but it was worth it. 'About 40 percent of Prilosec users made the switch to Nexium earning the drug over \$3 billion in 2003 and almost \$5 billion in 2004'.^{38,39}

Polymerase Chain Reaction

Polymerase chain reaction is a revolutionary method of amplifying small pieces of DNA *in vitro*. It is not so much a product or a process as a research tool that has multiple applications. It is popularly regarded as a true invention that can be traced to an individual, Kary Mullis, to a time (albeit approximate) and to a specific place: spring 1983 in the car he was driving at the precise location of the mile-marker 46.58 on Highway 128 in California.

PCR uses a naturally occurring enzyme called DNA polymerase to amplify sections of DNA rapidly, precisely and in staggeringly large quantities. DNA polymerase, a chemical well known at the time, performs various roles in the cells of living things including in the copying of DNA. Previously, the method used by scientists to copy DNA was cloning, which was basically to insert the desired piece of DNA in a microorganism and then to 'harvest' increasing quantities of the copied DNA as the microbes

with the added DNA reproduced themselves, something they do quite enthusiastically under the right conditions. Mullis's main contribution was to conceive of a way to control the action of DNA polymerase so that only selected pieces of DNA were copied, and then to launch and manage a cycle of repeated and exponential copying. As Paul Rabinow explains in his ethnographic study of Cetus Corporation, *Making PCR*, the revolutionary nature of PCR lies in that it

makes abundant what was once scarce — the genetic material required for experimentation. Not only is this genetic material abundant, it is no longer embedded in a living system. Cloning had made scarce genetic material abundant, but its obligatory use of living organisms as the medium of reproduction was also its limitation. PCR took a major step away from that dependency.⁴⁰

Or as Mullis himself explains, with a bit more flourish, in an article in *Scientific American*:

Beginning with a single molecule of the genetic material DNA, the PCR can generate 100 billion similar molecules in an afternoon. The reaction is easy to execute. It requires no more than a test tube, a few simple reagents and a source of heat. The DNA sample that one wishes to copy can be pure, or it can be a minute part of an extremely complex mixture of biological materials. The DNA may come from a hospital tissue specimen, from a single human hair, from a drop of dried blood at the scene of a crime, from the tissues of a mummified brain or from a 40,000-year-old woolly mammoth frozen in a glacier.⁴¹

Mullis's experiments to make PCR work in practice were not entirely convincing, and getting it to do so reliably was a team effort with various Cetus Corporation scientists involved. One of the biggest difficulties in making PCR efficient was that most DNA polymerase, including the one initially employed, is unable to withstand the high temperatures needed to separate DNA strands during each PCR cycle. Consequently, polymerase needed to be added each time. Mullis had proposed that a thermostable polymerase be used. Consequently, Cetus settled on a DNA polymerase from a thermophilic (heat loving) microorganism discovered earlier in the Yellowstone National Park, famous of course for its geysers, *Thermus aquaticus*. The task of purifying this chemical ('taq polymerase') was carried out in-house but not by Mullis. Once achieved, PCR had become sufficiently refined to be an extremely powerful research tool, and a commercial product as well.

The self-consciously eccentric and individualistic Kary Mullis plays the part of the inventor hero with great aplomb. And like so many past inventors of renown like Charles Goodyear of rubber fame,⁴² electrical engineer Nikola Tesla and plant breeder Luther Burbank⁴³ to name just three, Mullis never did receive his financial due, or so he believes.⁴⁴ There again, a share of a Nobel Prize doubtless made him feel a whole lot better. In his account of the invention, Mullis regarded it as a true flash of inspiration. He used the word 'eureka' three times and said that he exclaimed 'Dear Thor!' on realising at that moment he 'had solved the most annoying problems in chemistry with a single lightning bolt'.⁴⁵

Nonetheless, Mullis's PCR story did not convince everybody. The importance of Mullis's role, and the size of the creative leap that PCR represents, have both been questioned, including by some highly authoritative people. Perhaps the most prominent doubter was the late Arthur Kornberg, a Nobel prizewinner who was first to isolate a DNA polymerase, and who testified to a court that Mullis's 'invention' had been anticipated by earlier researchers including himself. In 1991, the court upheld the patents as did the Patent and Trademark Office after a re-examination.⁴⁶ Whether or not PCR was all that original, Mullis had done enough. The patent system is not about originality as such, nor is it about genius; it is about being first with something that has a practical, preferably commercial, application. The key patents protecting PCR were sold for the princely sum of \$300,000,000. And Mullis got his Nobel Prize.

Oncomice, Oncomammals ... and Oncoalmosteverything

In recent years, the United States, the European Union and Japan have sought agreement to harmonise international patent law so that all national and regional patent laws would be substantially identical in terms of definitions of novelty, inventiveness and industrial application and the permitted limitations and exceptions (see Chapter 9). This is anathema to many developing countries aware that the patent-related interests of countries vary in large part according to their levels of economic and industrial development, and mindful also that there are advantages to be gained from varied levels of patent protection in different jurisdictions.⁴⁷

What is often overlooked is that even among the developed countries, harmonising substantive patent law is far from easy. In no area is this more difficult to achieve than in the area of life science patenting. A good illustration of the challenge is the highly varied treatment of the patentability of one particular invention by courts and patent offices in two countries, the United States and Canada, and at the European Patent Office (EPO). This invention was the so-called oncomouse.

In 1988, the first-ever animal patent was granted in the United States.⁴⁸ The patent specification describes a mouse into which a gene has been introduced which induces increased susceptibility to cancer. The US patent was extremely, and unjustifiably, broad, claiming 'a transgenic non-human mammal' containing an activated oncogene sequence. Patents on the same invention were filed elsewhere including Canada and at the European Patent Office. In the United States, the product and process claims were allowed without any major modification and this was never challenged legally.

In Canada, though, the product claims of the equivalent patent were rejected by the Supreme Court on the basis that higher life forms cannot be classed as inventions in the way that machines, chemicals and microbes can be. Nonetheless, claims to the method of producing oncomice were accepted.⁴⁹

In Europe, things took an even more complicated turn with a very different final outcome. At first, the validity of the patent was rejected on technical grounds. On appeal it was granted in 1990.⁵⁰ Subsequent decisions upheld the patent but dependent on claims narrowed down from non-human mammals on the basis of Article 53 of the European Patent Convention, which stated that patents 'in respect of inventions the publication or exploitation of which would be contrary to ordre public or morality' cannot be granted. In 2001 the EPO's Opposition Division decided to restrict the product-related scope of the patent from 'non-human mammalian animals' to 'transgenic rodents'. In 2003, an interlocutory decision of the EPO's Opposition Division held the patent to be valid on the basis of the reduced scope but also affirmed that EPC rule 23d(d) which requires that patents not be granted in respect of 'processes for modifying the genetic identity of animals which are likely to cause them suffering without any substantial medical benefit to man or

animal, and also animals resulting from such processes', is applicable for drawing the appropriate scope of a patent such as the oncomouse one.

In July 2004, the EPO Technical Board of Appeal was again required to assess the validity of the patent. The Board's application of both the balancing test it had formulated in 1990 and rule 23d(d) resulted in a finding that the patent was valid but only on the basis of claims confined to 'transgenic mouse'.⁵¹

At the present time, negotiations have been going on at the World Intellectual Property Organization in Geneva on the text of a Substantive Patent Law Treaty. In light of the highly varied national interests and the inconsistencies even among the developed countries concerning patent rules and the way they are implemented, one must be sceptical of any agreement on a text of the treaty.

Large corporations operating in different markets have much to gain from harmonised patent rules and they are unlikely to give up without a fight. But their hopes may ultimately be confounded. Biotechnology gives rise to moral and ethical issues whose importance and relevance to patent law varies widely across cultures and legal systems. Consequently, the hope that all jurisdictions will deal with morality and ethics in their patent laws the same way may be over-optimistic. In this context, it is worth noting one of the arguments put forward by the dissenting Canadian Supreme Court judges in the Oncomouse case favouring the product claims: 'the mobility of capital and technology makes it desirable that comparable jurisdictions with comparable intellectual property legislation arrive (to the extent permitted by the specifics of their own laws) at similar legal results'. Desirable or not, this view was rejected.

Notes

1. Garfield (2001), 45.
2. *Ibid.*, 43–7.
3. Green (1915[1901]), 190.
4. Originally known as Meister, Lucius & Brüning.
5. BASF stands for Badische Anilin- & Soda-Fabrik AG.
6. AGFA stands for Aktien-Gesellschaft für Anilin-Fabrikation.

7. Dormandy (2006), 350; Jeffreys (2004), 11–15.
8. Stone (1763).
9. Dormandy (2006), 354.
10. Maclagan (1876).
11. Dormandy (2006), 359.
12. Kobrak (2002), 120.
13. Jeffreys (2004), 96.
14. This was discovered in 1874 at St Mary's Hospital in London by a team led by Frederick Pierce. It turned out to be 'one of the first drugs ever produced by modifying a natural molecule'. See Stone and Darlington (2000), 93.
15. Sneader (2005), 359–60.
16. Smith and Barrie (1976).
17. Rainsford (1999).
18. Vane (1971), (1994) and his Nobel Lecture — http://nobelprize.org/nobel_prizes/medicine/laureates/1982/vane-lecture.html. Also, Ferreira, Moncada and Vane (1971); Smith and Willis (1971).
19. Link (1959), 98.
20. *Ibid.*, 100.
21. Kresge, Simoni and Hill (2005); Last (2002), 4.
22. Link (1959), 103.
23. *Ibid.*, 105.
24. Perhaps the two most fundamental patents were: (1) US Patent no. 2,601,204 ('Process of lowering blood prothrombin level and lengthening clotting time with methylene-bis-hydroxy coumarin'), issued on 17 June 1952. This was a continuation of an application filed originally in October 1941. Campbell, Stahmann, Huebner and Link were named as inventors. (2) US Patent no. 2,345,635 ('Di-esters of 3,3'-methylenebis (4-hydroxy coumarin) and process of making them'), issued on 4 April 1944. This was filed originally in April 1942. Stahmann and Link were the inventors.
25. US Patent no. 2,449,866 ('Streptomycin and process of preparation'), issued on 21 September 1948.
26. US Patent no. 2,446,102 ('Complex salts of streptomycin and process for preparing the same'), issued on 27 July 1948.
27. Amyes (2001), 45–9.
28. *Ibid.*, 44–5.

29. Wainwright (1990) has advocated in favour of Schatz while Kingston (2004a) has defended Waksman.
30. Kingston (2004a), 441.
31. *Ibid.*, 459.
32. Ash and Schild (1966).
33. *Ibid.*
34. *Ibid.*
35. Black *et al.* (1972).
36. Freudenheim (1994).
37. Angell (2004), 79; Goozner (2004), 222; Law (2006), 76–8.
38. Manners (2006), 46.
39. In Europe, the company sought also to delay generic competition with Losec by means that the European Commission found in June 2005 to be an abuse of its dominant position. AstraZeneca was fined €60 million. *See* Lawrence and Treacy (2005).
40. Rabinow (1996), 1.
41. Mullis (1990).
42. Slack (2002).
43. Bugos and Kevles (1992).
44. His employers, Cetus Corporation paid him \$10,000.
45. Kary B. Mullis — Nobel Lecture. <http://nobelprize.org/chemistry/laureates/1993/mullis-lecture.html>
46. *See* Fore *et al.* (2006). The two patents were: US Patent no. 4,683,195 ('Process for amplifying, detecting and/or cloning nucleic acid sequences'), issued on 28 July 1987; and US Patent no. 4,683,202 ('Process for amplifying nucleic acid sequences'), issued on 28 July 1987. Mullis was named as sole inventor on the '202 patent, while four Cetus colleagues were added to Mullis's name as inventors on the '195 patent.
47. Dutfield (2008).
48. US Patent no. 4,736,866 ('Transgenic non-human mammals'), issued on 12 April 1988.
49. Harvard College v. Canada (Commissioner of Patents) 2002 SCC 76.
50. Decision of Technical Board of Appeal 3.3.2 dated 3 October 1990. T 19/90 — 3.3.2 *Official Journal of the EPO* 13, 476–491, 1990.
51. Decision of 6 July 2004. Case: T 0315/03 — 3.3.8.