

PREFACE

The average person taking a life-saving drug barely gives a thought to how it was developed...it is enough that the drug is here and is keeping that person alive. And, in truth, for some drugs the reality is that their background story is no more exciting or intriguing as how a new paint colour is developed in the paint factory laboratorythe usual mixture of logic, design skills, and trial and error....all very clever and professional, but hardly tinged with romance or drama that would warrant their story being told.

However, other life-saving drugs hold a fascinating story behind their development. No drug can be developed without a large amount of painstaking, methodical and often boring science, but where the fascination comes in is in the involvement of sheer chance (eg. **penicillin**) or amazing persistence and doggedness against all odds (eg. **insulin**) or a spark of genius or intuition, often set against a backdrop of human failings and personality conflicts. Often the existence of a drug responsible for saving countless thousands of lives can come down to the efforts of one or just a small number of individuals who swam against the tide of conventional thinking, or who succeeded against substantial odds, or who took considerable personal and professional risks, or who were in the end just plain lucky.

My first exposure to just how fascinating a drug development story can be came in the early 1980s with the introduction of the drug, **cyclosporine**. **Cyclosporine** completely changed the face of organ transplantation and remains to this day the single major reason behind the high success rates now achieved with kidney, heart, lung, liver and pancreas transplantation. At the time I was working in the field of transplantation research, and like a lot of others, I was looking to find better ways to control the rejection response that was holding back the successful use of organ transplantation across many diseases. Suddenly **cyclosporine** burst on the scene to much acclaim, providing a level of control of the rejection process hitherto not achieved, and single-handedly making liver and lung transplantation, in particular, practical realities. About that time I was fortunate enough to have the opportunity to meet Dr Jean Borel, the man most responsible for making the drug the success that it became. Meeting the man behind the discovery and hearing the story behind **cyclosporine** was inspirational. And that inspiration went a considerable way in influencing the development of the drug that is the subject of this book.

Cyclosporine was developed in the laboratories of the giant Swiss pharmaceutical company, Sandoz (now Novartis). In the 1950s, Sandoz, like many big drug companies, was searching for new therapeutic agents among the largely unexplored world of micro-organisms (the world of bacteria, fungi and moulds). The chance discovery of **penicillin** in the 1940s from an airborne mould that grew on a plate left overnight on a laboratory bench had sparked a major worldwide interest in micro-organisms as a potential source of new drugs, particularly new antibiotics. The world of micro-organisms, being the crowded, competitive world that it is, has meant that many of them have had to learn how to protect themselves from being overwhelmed. They do this by producing chemicals such as **penicillin** that keep other micro-organisms at bay. This approach remains to this day a major source of new antibiotics and antifungal drugs.

At Sandoz, they enterprisingly encouraged their employees worldwide to take plastic bags with them whenever they went on business trips and holidays. The idea was to have their

staff collect soil samples from distant places to be sent back to a central laboratory where they would be tested for the presence of previously unidentified micro-organisms. The next step then would be to see if those micro-organisms had the ability, like the penicillin mould, to ward off other bacteria and fungi.

In 1970 they had success. Two separate soil samples – collected by separate Sandoz employees in the USA and Norway – were found to contain a new strain of fungus. When this new fungus was grown in the presence of disease-forming fungi, it inhibited their growth. Sandoz chemists eventually identified the chemical causing this inhibition and named it **cyclosporine**.

The antifungal activity, however, was too modest to warrant any further interest, and that could have been the last that the world ever heard of **cyclosporine**. But a chance conversation between some Sandoz scientists over coffee saw it being passed on to another division within Sandoz that was looking at the effect of fungal compounds on the immune system. That chance conversation led to the true biological value of **cyclosporine** being revealed. This new group of Sandoz scientists discovered that **cyclosporine** strongly suppressed the immune system in animals. This was at a time in the late-1960s to early-1970s period when the medical world was becoming highly switched on to drugs that suppressed the immune system. Organ transplantation was beginning to emerge as a legitimate and common method of treatment for kidney and heart failure. Not surprisingly then, the discovery of **cyclosporine** piqued considerable interest within Sandoz in the drug's potential as an anti-rejection drug in organ transplantation. That potential eventually was confirmed by animal studies conducted over 1972-75 showing the ability of the drug to prevent the rejection of transplanted kidneys and hearts significantly better than current methods. There was some concern about the toxicity of the drug, but the standard anti-rejection drugs in use at that time in transplant recipients were themselves moderately toxic, so the excitement over **cyclosporine**'s potential continued because of its significantly more powerful anti-rejection capacity compared to standard drugs.

The first human trial of **cyclosporine** was conducted in healthy volunteers in 1976, but was stopped after the first few patients because it showed such poor absorption when given orally. The drug had proven to be adequately absorbed from the stomach in animals, but something about the human stomach was preventing its take up. That is when the disappointment and nerves set in. The poor oral absorption, on top of the toxicity that had been observed earlier in animals, led senior executives in Sandoz to seriously question the commerciality of the drug. They eventually decided to abandon any further work on the drug.

At this point, Borel and a small group of colleagues decided to take matters into their own hands. Dismayed by the decision of senior management to abandon work on a drug with such enormous clinical potential, they quietly continued to see what could be done to resurrect the program. They realised that the critical thing to be overcome was the absorption issue. They needed to get the drug into such a form that most of it would be absorbed when swallowed by humans. This they eventually achieved, proving in animal studies that the new formulation was considerably superior to the old formulation. That still left the issue of toxicity, and that of course raised the possibility that this might even become more of a problem now that they could get the drug into the body in even greater levels.

Borel and two colleagues then decided that the only way to get the program back on the official rails was to do something dramatic. They decided to dose themselves with the drug.

Self-experimentation has a long and proud history in medical research, and advances in a number of key areas such as vaccines and anaesthetics owe a lot to early workers subjecting themselves to weird and wonderfully dangerous experiments. It is one thing for lone operators to self-experiment, but it is an entirely different thing for scientists within a company structure to go against rules and to self-experiment. I suspect that Borel subscribed to the adage that it is better to seek forgiveness than to seek permission, because he and his two colleagues dosed themselves daily with **cyclosporine** over several weeks. At the end of that time, they had proved that the new formulation was well absorbed and well tolerated and completely without the side-effects than had been seen in animals.

While some would regard this act as foolhardy because of the significant risk of self-harm, others would say that it represents a level of scientific conviction that all too few scientists are prepared to take. In any case, it proved to be the watershed that led to the drug eventually becoming a standard form of anti-rejection therapy for most transplant patients worldwide.

I found that total belief shown by Borel and his colleagues in **cyclosporine** to be inspirational. Some years later when involved in the challenges of developing a new drug technology that eventually spawned **phenoxodiol**, I had good reason to think back on that single-minded determination shown by the Sandoz scientists and to take heart from their determination.

So why does the **phenoxodiol** story warrant being told? Well, in part because I have the firm belief that it, and the family of drugs that it has spearheaded, will lead the way in a revolution of how we treat and manage cancer. But also in large part because, like the **cyclosporine** story, it's pathway or development is a form of scientific odyssey that some people may find interesting.

Phenoxodiol is truly an anachronism in the world of cancer therapy – a drug that can kill cancer cells without doing harm to the body. But it was an anachronism that almost meant that the drug never got developed ... a concept so difficult to embrace that the financiers who are so essential to ensuring that drugs get developed in the first place, and the pharmaceutical industry which is so essential to ensuring that drugs eventually get to patients, displayed a level of scepticism bordering on indifference, to the extent that if not putting the whole development process in jeopardy, at least made it harder and longer to bring such an important new drug to market. The reason that the drug eventually will become an important new tool in medicine is due to the dedication of a small number of scientists and administrators who took on significant challenges to ensure the drug's success. Those technical challenges, against a backdrop of the travails that are common to small biotech companies, are what I believe make for an interesting story.

The **phenoxodiol** story has had its share of frustration, exhilaration, tedium, stimulation and exhaustion...but overall, it has been compulsive.

Graham Kelly