

THE CONDUCTORLESS ORCHESTRA

To those in the business, the name 'Dr Paul' is synonymous with an insightful, integrated and, most of all, successful approach to the subject of drug discovery. His death will be mourned in particular by those seeking a return to the 'old-fashioned' principles of drug hunting.

Paul Janssen, who died unexpectedly in Rome on 11 November, used to compare the different disciplines that make up the drug discovery and development process to the sections of an orchestra. His vision for the ideal drug discovery team was of a group of people with widely differing skills operating in complete harmony with one another, and he saw his role as being to lead that team towards a melodious result. His integrated view of the business of discovering drugs was completely at odds with the modern fashion for creating drugs from serially linked, independently managed business units, each of which focuses principally on improving the efficiency of its own particular portion of the pipeline. With Janssen's death, drug discovery has lost one of the few remaining maestros of the art.

One of the most successful drug hunters of all time, and arguably the most prolific drug discoverer of the latter half of the twentieth century, Paul Janssen began synthesizing drug candidates in the factory of his family business more than 50 years ago. From the very start, Dr Paul, as he became known to all who worked with him, believed in the principle that R&D operations should not be a drain on the family resources, but should pay for themselves. His goal of turning his experiments into a profit centre was helped by the fact that the fifth compound he synthesized, ambucetamide, turned out to be an effective uterine antispasmodic, and made it to market in 1955 as Neomeritine, just two years after the initial synthesis. Indeed, 5 out of the first 1,000 compounds synthesized became marketed drugs, an early indication of the remarkable 'nose' that Dr Paul had for finding drugs, and enough of a boost to the finances to allow the company to grow rapidly. In 1961, the Janssen family business merged with Johnson & Johnson, and the drugs kept pouring out.

His stated method of building up a drug discovery team seems highly unorthodox when compared with today's company culture; rather than looking for people to fulfil particular functions, he tried to attract intelligent people whatever their expertise, believing that their

inquisitiveness would ensure that they found a way to contribute to research efforts. Keeping a healthy regard for the contribution of serendipity, he believed that research cannot be organized in a pre-arranged fashion, and he therefore allowed his staff to evolve their own ways of doing things. Of course, his leadership, and indeed his daily contact, at least in the early stages, with all his researchers, was credited as being the guiding influence that kept all this research on track, and prevented the energy being dissipated in unprofitable 'Brownian motion'.

For the forty years following Dr Paul's first forays in the laboratory, his company produced an average of around two new drugs each year, among them ground-breaking treatments for intractable pain (fentanyl and its congeners) and mental illness (haloperidol and risperidone). But as the drug discovery scene changed, so this most involved of research directors began to find himself increasingly isolated from the people he was trying to direct. A little like the conductor on the podium at one of the mass performances of Handel's *Messiah*, at which thousands of people turn up and perform with no prior rehearsal, Dr Paul had less and less control over whole sections of his company, which were intent on going their own way. By the early 1990s, Dr Paul had all but parted company from the enterprise he had built, and concentrated instead on recreating the sort of small, interdisciplinary research unit that he felt gave rise to the most productive science. Since its creation in 1995, his Center for Molecular Design in Vosselaar, Belgium, with just 14 staff in total, has been developing a novel family of non-nucleoside reverse transcriptase inhibitors for the treatment and prevention of HIV/AIDS. Their considerable success with a range of dianilinopyrimidine (DAPY) analogues looks set to prove that Dr Paul hadn't lost his touch, and emphasizes his mantra that being big isn't necessarily an advantage in the search for new drugs. Chamber orchestras can make sweet music too, when in the right hands.

“Drug discovery has lost one of the few remaining maestros of the art”