A Personal Perspective on Dr. Paul Janssen

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Dr. Paul Janssen was the most prolific drug inventor of all time. Some people will point to the incredible number of drugs that he invented and marketed; some people will note the huge revenues that his drugs earned for Janssen Pharmaceutica and Johnson & Johnson; some will marvel at the wide range of his inventions in psychopharmacology, neuropharmacology, gastroenterology, cardiology, parasitology, virology, immunology, anaesthesiology, and analgesia; others will draw attention to his exceptional managerial skills in leading and motivating and rewarding his very large R&D group; and more business-minded people will, with a mixture of admiration and envy, applaud his negotiating and deal-making skills in the marketplace. However, I want to emphasize and draw attention to the psychology of his inventiveness that, I believe, was the basis of his unique fecundity. Dr. Paul has much to teach Big Pharma about research and development today. But I know from conversations I had with him in recent years that he had lost faith in the industry's desire to learn from his wisdom and insight.

Dr. Paul told me that when he graduated in Medicine, his father offered him the pharmaceutical manufacturing company that he had spent many years building up into a successful business. Paul's reaction was that he would be excited if he could use the resources of the business to do research. From the start he had a conception, an idea that was not wishful thinking, not a woolly "wouldn't it be nice if ..." sort of idea, but an eminently achievable and potentially useful idea. As a medical student, he had learned about pethidine, a new drug that had been introduced into medicine in 1939. Pethidine (meperidine in the U.S.) had been introduced into medicine as an atropine-like antispasmodic/antidiarrhoeal agent but clinically had been found to be an addictive morphine-like analgesic. He was attracted to pethidine because he knew that it was a piperidine derivative and that piperidine chemistry was fairly easy. He wanted to see if he could separate these two properties. He had a chemical starting point and two appropriate bioassays: the Straub mouse tail test for opiate activity and the electrically driven guinea pig ileum in vitro for antispasmodic activity. He eventually succeeded in the invention of loperamide, an antidiarrhoeal drug, and fentanyl, a highly potent analgesic, both of which are still in use today. As far as I know, Dr. Paul never started a project without a conception in his head, a conception that not only specified a chemical starting place, a "lead" molecule, with appropriate bioassays but also embodied foresight of how his invention would deliver clinical utility.

Given his conceptual chemical lead, he and his team would systematically synthesize analogues or derivatives of the lead and then evaluate them in the chosen bioassays. Whatever the result, any result would suggest a new molecule to make and test. Iterative synthesis, bioassay evaluation, and test feedback would gradually build up a picture of structure−activity relations. The whole process of forced chemical mutations that are tested for fitness in a biological environment is like Darwinian evolution. The one certain feature of this cycling is that it is a slow process. The whole process has to be driven by intense concentration and relentless commitment. Concentration is necessary to allow the evolving complex picture to be clear in the mind so that timely judgments can be made about when to continue a line of chemical thought and when to change direction. On the other hand, commitment is necessary to stay the course, to see it through. From my viewpoint, Dr. Paul's intense concentration and passionate commitment were unique in our industry. Finally, there is creativity. Creativity has a special meaning for inventors. The creative act of invention is to judge when the product is "fit for its purpose". Good judgment comes partly from experience, partly from imagination, and partly from a kind of aesthetic intuition. Dr. Paul was endowed with all of these qualities.

I take this combination of conception, concentration, commitment, and creativity to be the psychological determinants of Dr. Paul's success as an inventor. Dr. Paul, of course, managed his own mind. However, these are inherently manageable qualities. Today's industrial research managers could learn from him well. They could decide to select only concept-driven projects as opposed to today's norm of technology-driven projects. Concept-driven projects have two managerial advantages. First, ideas, coming as they do from individuals rather than groups or committees, identify the natural project leader. Second, that leader will almost certainly look for the simplest (and cheapest) technology that will be least ambiguous in solving the problem.

Concentration and commitment are the toughest managerial challenges in new drug research. A natural tendency in Pharma research labs is to dissipate energies into smaller and smaller groups. Today, molecular biology and genetics offer investigators an unlimited number of targets. Every red-blooded investigator wants to concentrate on his own target. The upside may be enthusiasm; the downside is likely to be superficiality and a loss of tempo. Managers, as exemplified by Dr. Paul, need to provide the catalytic energy to focus team efforts.

Commitment is the biggest problem of all today. Once Dr. Paul got his mind on a new concept, he never gave up on it. Research people get tired and want to quit when the breaks are not coming; money people get impatient when the breaks are not coming. The problem is that the rhythm of research is slower than the rhythm

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of money. Only courageous managerial decisions can bring them into some kind of harmony. Dr. Paul was a lesson to us all in courageousness in research and development.

Of course, Dr. Paul did not invent the iterative, evolutionary process in drug invention. He followed a great tradition begun by Paul Ehrlich over 100 years ago. Pursuing his concept of "magic bullets", Ehrlich systematically changed the structures of organic arsenical dyestuffs and tested them in rabbits infected with *Treponema pallidum*, the then-recently discovered cause of syphilis. He changed the structures using chemical ideas that he had developed in a lifelong study of dyestuffs chemistry. His head was full of chemically reactive groups that he called "chromophores". Eventually, the 606th compound, Salvarsan, was found to be an effective agent with a satisfactory therapeutic index. Basically, Ehrlich was the father of medicinal chemistry. And Dr. Paul was a learned disciple. As Dr. Paul grew in experience he, too, filled his head with chemically reactive groups that he called "pharmacophores". I often watched him at meetings, when bored with the proceedings, finding solace inside his head as he doodled new chemical compounds!

Starting in 1927 Gerhard Domagk, inspired by Ehrlich, systematically made and tested azo dyes for efficacy against streptococcal infections in mice. He eventually found that the dyestuff prontosil red inhibited the growth of these organisms. Prontosil red was the forerunner of the sulfonamides and the start of the chemotherapeutic revolution. In the 1930s, Daniel Bovet used Ehrlich's method to develop new drugs that antagonized histamine, a natural, physiological chemical. The invention of these so-called antihistamines started a new wave in medicinal chemistry based on physiological receptor-seeking hormones and enzyme substrates. In the 1940s, George Hitchings and Gertrude Elion made new drugs related to purines and pyrimidines by using the time-honored iterative method of synthesize, test, synthesize, and so on. When I started at ICI in 1958, I was totally ignorant of the work of these giants. We, too, began from physiological molecules, first adrenaline and later histamine. A key point here is that Ehrlich (1908), Domagk (1939), Bovet (1957), Hitchings (1988), Elion (1988), and Black (1988) were awarded Nobel Prizes, whereas the greatest of us all, Dr. Paul, was not. He was certainly nominated several times, but perhaps he did so much that his work could not be easily summarized in a sentence or two. All I know is that his life's work was Nobel Prize worthy. In his will, Alfred Nobel commanded that the interest from his estate should be distributed in the form of prizes to those who "shall have conferred the greatest benefit on mankind". By any yardstick, Dr. Paul must have been a great candidate.

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