



feature

The conductor and his orchestra

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The causes of declining productivity in drug discovery are often attributed to difficulties in finding new and interesting drug targets, stricter regulatory requirements and enormous development costs. Less often mentioned is the stifling hierarchical organization of research in many large companies and their reluctance to provide freedom to competent and daring researchers to excel themselves in their chosen field.

This article deals primarily with the human factor of successful drug discovery by setting Dr Paul Janssen as a role model of inspirational leadership. He founded a pharmaceutical research laboratory that, arguably, became the most successful invention factory for medicines of all time. The human aspects of this successful research venture are described here from the author's first-hand experience of Paul Janssen's leadership and from testimonials of his former employees.

Dr Paul Janssen's research enterprise

Paul Janssen studied medicine and further educated himself to become a first-class medicinal chemist. His dream was to invent novel synthetic medicines by means of simple laboratory experiments, and his idea was to obtain interesting patents rapidly and reinvest the proceeds from these into his research. When he started out in 1953, in a garage-like laboratory in his father's factory, few people believed this could be done. Material conditions during the early research period were rather rudimentary and Janssen himself frequently went out early in

the morning to collect rabbit intestines from a local butcher for the pharmacological experiments. But after work, Janssen and the more sporty members of his team found time and energy to play soccer in a local league competition (Fig. 1). Togetherness under strained conditions forged a nucleus of loyal coworkers on which Janssen could rely for the continuation of his endeavor [1,2].

In 1961, Johnson and Johnson acquired the Janssen Company, when it had already achieved major inventions in analgesia, psychiatry, allergy and gastro-intestinal diseases. The acquisition of the company was welcomed by its founder as a kind of life insurance for his personnel. Many people who had worked with Janssen from the very beginning were self-made people who had tied their life and career to Janssen's enterprise. He did not want to leave them unprotected if something tragic were to happen to him. The agreement also provided Janssen with freedom and autonomy for his research. By the time of his retirement he had invented 80 novel medicines, mainly for the treatment of pain, psychosis, allergy, parasitic and fungal infections, gastro-intestinal and cardiovascular disorders. Five of these were included in the List of Essential Medicines of the World Health Organization and several of them reached blockbuster status. After his retirement, Paul Janssen continued doing research in the semi-autonomous Center for Molecular Design of the Janssen Company. There, with a small international group of scientists and the help of a supercomputer, he invented a new generation of anti-HIV compounds.

Paul Janssen died suddenly in 2003 while attending a conference in Rome. He will be remembered as the most prolific drug inventor of all time [3,4]. When asked about his role in the organization, Janssen always replied that he considered himself merely as the conductor of an orchestra. He remained the conductor of his ensemble, even when it had grown from a small jazz combo to a large symphony orchestra [5].

During its rapid expansion in the 1960s many visitors to the Janssen laboratory were puzzled by its success. The premises were rather austere, the equipment was largely homemade and most researchers lacked academic degrees. Yet, scientific productivity in terms of publications and patents was, in comparison to other laboratories, exceptionally high [6]. The key to this success lay to a large extent in Paul Janssen's leadership style and the characters of those that were employed by him [7].

The use of 'farmer's sense'

Paul Janssen grew up in a predominantly rural region in the North of Belgium (Kempen or Campines) and inherited the stubbornness, tenacity and sense of freedom of its inhabitants, who are characteristically critical of what others say and do. They prefer to form their own opinions and, though used to hard labor, they generally do not like to be told what to do. They also say 'I will believe it when I see it with my own two eyes'. Paul Janssen once remarked that the decrease in the number of farmers has led to less common sense [8]. By cultivating 'farmer's sense' he meant that scientists should above all seek truth by relying on evidence and sound judgment.

Intellectual authority was strictly rejected at the laboratory. Janssen always insisted on examining experimental raw data as they were produced in the laboratories before accepting any interpretation of them. When compounds

**FIGURE 1**

The Janssen soccer team of 1963 showing Dr Paul Janssen in the middle of the first row (reproduced with the permission of Janssen Pharmaceutica NV.)

went into clinical testing, he or his staff regularly went to hospitals to personally check the record taking.

Janssen always thought through all the implications and ramifications of a plan. This involved the synthesis and testing of compounds, their expected physical and biological properties, the various risks and benefits up to regulatory approval, production, distribution and sales.

Finally, what mattered to Janssen was the courage and determination to pursue a plan once it was agreed on to go ahead with it. If the submitter showed competence and appeared determined to persevere when the inevitable difficulties arose, as they always did during the course of a research project, then Janssen would never forbid the 'go ahead'. He would say 'I'm not convinced, but since you are so determined I will give you the resources to pursue your plan.' Janssen valued courage and perseverance in people even more than intelligence and proficiency. He often stated that there is no merit in being courageous when everything goes well and that the real stamina of a person appears when he is with his back against the wall and

everything seems to be lost. Later in life, Janssen admitted that many of the great inventions in his laboratory came about this way. In new drug research, character is more important than intellect [9], and the recognition of the human side of invention leads to the right drug discovery spirit [10]. Tenacity coupled with hard work, dedication and never-ending curiosity of Janssen scientists has led repeatedly to important breakthroughs. For example, the discovery of the atypical antipsychotic risperidone followed 26 years after that of haloperidol [11]; the broad-spectrum antimycotic itraconazole was invented 13 years after miconazole; etravirine, a new generation anti-HIV compound, was found after 12 years of antiviral research [12]. In all these cases, most scientists and technicians who had participated in the early start of research also witnessed the later breakthroughs. Membership of Janssen's orchestra was generally for life.

The flat organization

Owing to its early success Janssen Research rapidly expanded from the initial group of four coworkers to ca. 200 in the early 1960s, working

in more than ten different therapeutic areas, including analgesics, antipsychotics, antispasmodics, antihistaminics, antidiarrhoeals, antiparasitics, antimycotics, gastroprokinetics, cardiovascular agents and several others. This caused Paul Janssen to reflect on how to organize his research, which had naturally divided into more or less autonomous units that were composed of pharmacologists, biologists, organic chemists and laboratory technicians.

From his early contacts with pharmaceutical companies that licensed his inventions, Janssen had observed that most of them had (and many still have) a rather pyramidal research organization with several layers of command between the director and the people that worked in the laboratories. He considered that this was not the most effective way of doing breakthrough research and decided to do it 'the other way around' by keeping his organization as flat as possible. He did not want his employees to report to him nor to anyone else. He resisted the introduction of organization charts, committees, functional titles and job descriptions [13].

The flat organization worked effectively because of Janssen's almost continuous

presence. His working day was mostly filled with his rounds through the laboratories. Moving from one place to another, Janssen made everybody aware of what was going on in the different areas of research. He often brought researchers from different areas together if he thought their synergy could be beneficial. The flat organization lacked formal priorities, deliverables and deadlines. Even the concept of pipeline was unknown.

Janssen made a distinction between workers that were paid by the hour and researchers that were paid for performing their (mostly self-assigned) tasks. There was no set limit to the amount of time the researchers should spend on a particular task. It often involved working late at night and during weekends. Janssen made no secret of the fact that he abhorred the word vacation, which he understood only in the sense of 'having no work to do'. This flat organization selected out people that needed little supervision, could bear multitasking and were able to define job content for themselves.

The purely flat research organization described above lasted until the mid-1980s when the Janssen Company had created an international structure of production, marketing and sales, eventually operating in 40 countries and employing over 22,000 people worldwide. This caused the gradual transition to a more hierarchical organization with functional titles, job descriptions, reporting lines, pipeline, stage-gating and decision making by committees. By that time the research organization had grown to over 500 scientists, technicians and supporting staff (not including those in development), and had kept a steady pace of delivering products which were developed, approved and introduced at an average rate of 2 or 3 per year.

Bottom-up works well when the top is small

Janssen expected his employees to come forward with their own ideas and proposals. He organized his research around competent and trusted scientists, while continuously critically examining everything that was proposed to him [14].

When meeting with Janssen, his first words would invariably be: 'What's new?' Whatever the answer, it would be challenged with: 'Is it true?' or 'Do you really believe it?' As Janssen made a daily round through the labs his people had usually prepared themselves for his visit and the question 'What's new?' with tables and graphs of results from the previous day. Often people saved some 'news' for that occasion when they were in short supply of it. There was no excuse for not being fully concerned with science and research, as

formal meetings were forbidden and administrative chores were kept to the bare minimum.

One can imagine the enormous energy that is released when a system is gently tapped at its resonant frequency and its parts start to vibrate in synchrony. Think of the Tacoma Narrows Bridge swaying to destruction by successive gusts of wind. In a state of resonance the oscillations of the various parts of the system synchronize and mutually amplify their activity [15]. This way, many employees of Janssen felt that they had been able to exceed the limits they had set for themselves. This resonance was just as essential for Janssen himself as for his employees. The conductor and the orchestra depend on each other.

The success, however, was not obtained without sacrifice. Life as a scientist or inventor can be demanding, not only on him or her, but also on partner and children. Continuous strain and workload have occasionally caused personal and familial problems. When they arose, Janssen did have a great concern and understanding for these situations and he was always supportive when his collaborators went through a difficult period in their life. Apart from being an inventor of medicines he was also a physician and humanist. He was to his staff a '*pater familias*', demanding, fair and caring.

Breakthrough inventions are made by people, not by committees

Janssen was convinced that the greatest source of inspiration was in the people that had joined him. He was able to spot talent and opportunity. In fact, he had as good a nose for promising people as for interesting molecules. He especially looked for talented persons whom he could mold to his bottom-up way of conducting research and who were capable of acquiring the necessary skills and background by themselves. He went as far as to ask a local high school for intelligent students that might choose to work with him rather than going to the university.

Interesting people were often hired without a vacancy for a specific position. Janssen claimed that the organization must adapt to the people that came to join it and not *vice versa*. In this respect the organization is more like a living organism than a predesigned mechanism. A striking example can be found in the hiring of former colonials that had returned to Belgium after the declaration of independence of Belgian Congo in 1960. They had worked for many years in the sanitary and veterinary services of the former colony and acquired considerable experience in tropical diseases. Among these were parasitologists and mycologists who within

a few years produced synthetic, highly potent and practically atoxic antiparasitic and antifungal drugs. Innovation requires scientists in a stimulating environment [16] and shared beliefs in an organizational culture [17].

Discussion and conclusion

It is often stated that the continued welfare and well being of the world depends to a large extent on its capacity to innovate and invent. There is no shortage of well-intended policies for the promotion of research by providing resources, education and motivation. Paul Janssen was convinced, however, that the best policy in this case is to identify inventive people and give them the means and the freedom to do what they feel they must do [18–20].

It may be argued that success stories like Janssen's are exceptional and that the environment for industrial research has changed because of increased legislation, regulation, risk aversion and organizational complexity. It may indeed be no longer possible for a single person to oversee the whole of research and development of a pharmaceutical company. Paul Janssen had realized that development may require a style of leadership that is different from that of research. He often stated that research comprises all what one has to do to convince oneself of the originality and validity of an invention and that development must convince the rest of the world. Obviously, the latter may take more time, effort and discipline than the former, and the flat organization as described here was primarily conceived by Janssen for his research activities.

Small research organizations may be more apt to adopt Janssen's concept than the larger companies that often arise through mergers and acquisitions. This may be particularly true for young biotechnology companies [21]. Nevertheless, the concept worked well at the height of productivity of Janssen Research, when the laboratory had expanded to over 500 scientists, technicians and administrative staff. At this stage the laboratory had crystallized around key activities guided by competent and trusted scientists, whom Janssen referred to as '*primus inter pares*'. Notwithstanding the relatively large size of the laboratory, it was still possible for Janssen to exercise his management by walking around. To that effect he had appointed a coordinator, who had no formal authority, but whose job it was daily to collect and digest the results produced in the various units.

Gifted and talented people like Paul Janssen may be hard to find, as large organizations do not as a rule select for stubborn, independent

leaders that want to realize a great dream of their own. But when these organizations are prepared to give up part of their control and provide autonomy and resources to talented scientists with leadership capability the rewards can be extremely great. Examples thereof can be found in the biographies of Nobel Prize winners like George Hitchings, Gertrude Elion and Sir James Black. As stated above, it takes a good nose to identify these exceptional people, just as it takes a good nose for discovering and inventing interesting medicines.

The question remains whether Janssen's highly successful style of leadership would still be applicable today. Environmental conditions change over time, but human nature has not changed over the past few decades. It probably has not changed much over the past 10,000 years. When natural leaders are given the freedom to think, dream, play and dare they will attract those that are inspired by them to excel and surpass themselves [19]. Much depends on the climate that is created by industrial and governmental organizations, especially their willingness to facilitate independent and autonomous researchers and refrain from excessive bureaucratic control over them.

There is no reason why there should be less enterprising and competent people with a great idea in their mind than before. There may be more of them now, given the recent progress in medicine, biology and technology and the opportunities they present. In the pharmaceutical industry as well as in other sectors breakthrough innovations are often made by people that want to pursue an idea, realize a great dream or find an answer to a burning question, despite the many obstacles and difficulties that lie in their way. In the end they will say in the words of Sir Winston Churchill that 'this was their finest hour' [22].

A leadership style like Janssen's, which takes into account the human aspects of research offers a competitive advantage over more hierarchical systems and provides a better chance for success. After all, it takes a good conductor and an inspired orchestra to play beautiful music. In the case of Janssen Research, conductor and orchestra have played well!

Acknowledgements

The author is indebted to Sir Robert Stouthuysen, former General Manager and President of the Board of Janssen Pharmaceutica NV, and Prof. Koenraad Debackere, General Manager of the Catholic University of Leuven for providing valuable insight into the management of science and technology. Guido Theunissen is thanked for providing useful information on the history of Janssen Research. The editorial help with the manuscript of Ann Turner and Prof. Eddy Arnold is gratefully acknowledged. The author also acknowledges the many constructive remarks of the reviewers, which have improved the style and content of the manuscript.

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