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Successful Pharmaceutical Discovery: Paul Janssen's Concept of Drug Research

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The pharmaceutical industry is going through a difficult period. Research productivity in terms of new products brought onto the market is declining, while research costs are increasing year on year (Smith et al., 2003; Cuatrecasas, 2006). During the past decade pharmaceutical research has become increasingly dependent on processes, stage-gating and market orientation. The result has been a shift of attention from the individual researcher, patient and physician to hierarchical management structures. While the latter may work well in incremental innovation, such structures are far from optimal for fostering the type of environment that most often leads to breakthrough research.

One may well ask what is wrong with today's pharmaceutical research. But, it is also worthwhile asking what was right before the present predicament arose. Take Janssen Pharmaceutica for example, which produced 79 novel medicines over a period of 40 years. Its key to success can be attributed to a large extent to its founder's, Paul Janssen, unique organization of research. His concept of how to drive creative drug discovery focused around the dual principles of "organizing around competent people" and "continuous critical questioning". The following description of this approach to organizing research is heavily indebted to the personal experience of the first author, who worked with Paul Janssen for over 40 years.

1. Introduction

Janssen relied on two basic criteria for effective research, both of which are frequently at odds with current practice. Firstly, he believed that research should be centered around competent people rather than around predefined processes.

Secondly, the specific goals of research were not to be imposed, but should instead result from continuous critical questioning. Janssen believed that the criteria used for research were necessarily different from those applied to development, production, marketing and sales.

Janssen understood that the nature of research is such that discoveries and inventions are often unplanned and unpredicted. They are made by self-motivated and inquisitive people who are encouraged to persevere in the face of adversity. Good researchers do not need to be controlled, nor do they have to formally report on their work. Ideally researchers must be given the freedom to pursue their own research interests.

Thus the organization needs to adapt to the competences of the people that are present, or that may join the organization, rather than the other way around. In this respect the research organization behaved more like a living organism than a preprogrammed machine. Having observed the predominantly pyramidal structures of research organizations in large pharmaceutical companies, with numerous levels between the director at the top and the scientists at the benches, Paul Janssen chose to organize his research differently. As a consequence, the organizational structure was as flat as possible, without reporting levels, titles, committees and status symbols.

As long as such an organization remained small, research was centered around a competent researcher with leadership capability. As it grew, the organization was broken up into separate specialized research units. In this case, a central role was assumed by Paul Janssen, a highly competent research director, who had a broad scientific background and deep human interest. The director was like the conductor of an orchestra. As leader, he was in direct and almost permanent contact with his collaborators, synchronizing their activities and creating a harmonious resonance among the various units. Walking the floors of the laboratories, the main function of the director was to manage by prompting his collaborators to come forward with ideas and propositions, and by critically questioning the ongoing research and the commonly perceived goals. The relationship between the leader and his collaborators was therefore strongly based on trust and recognition, rather than on fear and compensation.

Against this background, it is important to note that Janssen envisaged the research organization as a profit center, rather than a cost center. Its primary mission was to make patentable inventions, whose profits could be reinvested in the research organization.

2. Paul Janssen, the man behind the concept

Paul Janssen was born in 1926 in Turnhout, a provincial town in the Northern part of Belgium. His father was a general practitioner who had founded a pharmaceutical factory in his hometown where he produced classical medicines

for the local market. After obtaining his medical degree Paul Janssen specialized in pharmacology under the direction of the Nobel laureate Corneille Heymans. In 1953 he set out to realize his great dream, which was to invent new medicines by synthesizing large numbers of compounds and by determining their pharmacological properties in simple but reliable assays. His father allowed him to use a kind of garage in his factory as a laboratory and assigned four young workers to help out. During the first three years the group had synthesized and tested about 800 new chemical compounds, of which eight came to the market as medicines. Number 79, an antispasmodic compound (Priamide^{TM}) would have been called a blockbuster compound by present-day standards. The drug was prescribed for dyspepsia and stomach ulcers. Given the changes in eating habits in the post-war period and the concomitant gastro-intestinal side effects, the product rapidly became very successful. Not having production, marketing and sales facilities at his disposal, Janssen provided licenses on his inventions to major pharmaceutical companies. This generated a steady and substantial income in the form of royalties on sales. Initially all income was invested immediately in the research laboratory, according to Janssen's motto: "First comes research, then business".

Due to the initial success and rapid expansion of his research, Janssen transferred his laboratory to the neighboring village of Beerse. In 1961 Johnson & Johnson acquired full ownership of Janssen Pharmaceutica and nominated Paul Janssen as its research director until his retirement. An important part of the agreement guaranteed that Paul Janssen would have full autonomy over the research and development of the compounds that he invented. The deal proved to be extremely beneficial to all parties and the Janssen laboratory grew exponentially both in personnel, scientific output and commercial value.

Over the course of four decades Janssen introduced a flow of 79 novel medicines, including antipsychotics, antifungals, antiparasitics, analgesics, gastro-intestinal agents and cardiovascular drugs onto the market. The major milestones and the people that played an important role in achieving them have been amply described elsewhere (Schwartz, 1989). The Janssen laboratory contributed also to basic and applied science in such diverse areas as behavioral and biochemical pharmacology, toxicology, pharmacokinetics, clinical studies, data processing, statistics and clinical research. At its peak, the Janssen laboratory produced more than 200 scientific publications per year.

In 1991, at the age of 65, Paul Janssen had to retire from his function as research director. Shortly thereafter he founded the Center for Molecular Design, an autonomous unit within the Janssen research division. It was set up as a virtual laboratory dedicated to the research and early development of medicinal compounds, mainly in the field of HIV. The center was located apart from but close to the main site, and Janssen acted as mentor to a small research group

that functioned according to his proven concept. Not surprisingly, the center was successful and contributed several novel compounds that are now in the late stages of development.

Paul Janssen, arguably the most prolific drug inventor of all time (Smith et al., 2002; Black, 2005), died suddenly while attending a scientific conference at the Pontifical Academy in Rome in 2003 (Lewi, 2004).

3. A typical day in the laboratory with Dr. Paul

Dr. Janssen's typical working day started by meeting the coordinator of research. The latter's role was to collect the data from the various units and to produce a daily digest of them. This way Paul Janssen was brought rapidly up to date on the latest findings and the problems that needed his attention before he started his daily rounds of the laboratory. He loved to have immediate contact with his personnel, be they head of research, laboratory technicians or secretaries. He often knew their family situations, hobbies and special interests. All employees addressed him as "Dr. Paul", which was intended as an affectionate form of respect towards the head and founder of the laboratory.

If something important came up, Paul Janssen wanted to be the first to be informed. Every time one happened to encounter Janssen in one of the many corridors of the laboratory one would be arrested with the question: "What's new?" Paul Janssen requested his collaborators to come forward with interesting ideas, proposals and plans. These could be original thoughts or reflections on recent publications. He did not like people that waited for orders to carry out, nor did he require them to give formal reports about their progress.

Janssen used to start his journey through those laboratories where he knew from his morning briefing with the coordinator that interesting developments were taking place. Normally, people would have prepared their results from the days before in the form of tables and graphs and discussion followed from there. After about a quarter of an hour, Paul Janssen would offer some advice or encouraging words and leave. Then it was not unusual for a scientist to take a spoon or something and give a few brief taps on the tubes of the central heating system as a warning sign for those working further down the corridor: take care; be prepared; he's coming; don't get taken by surprise and see to it that you have "something new" ready at hand. The worst punishment was when Janssen no longer asked "What's new". This meant that he no longer considered the person as fitting his pattern of research; a serious warning sign.

In the afternoon most of Janssen's time was again spent in the laboratory, but interleaved with receiving outside visitors. Notwithstanding this busy schedule, he was readily available to his collaborators for discussions, briefings and requests for advice. The latter usually was dealt with in a very brief and simple manner. Janssen's advice was often: "Act as if it was your own money at stake". If an

urgent or important matter came up, Dr. Janssen's secretary would find a spot between walking rounds or visits when the issue could be resolved. Formal meetings were never held and committees were nonexistent within the laboratory. Janssen only had to make decisions in the case of lack of consensus between him and the scientists, which was exceptional.

In-between walks around the laboratory and visits, Janssen scanned the many professional journals that his secretary arranged for him on a table in his office. On the cover he noted names of collaborators and reams of page numbers of articles that were within their domains of interest, always with the remark "to be discussed". There was no place for scientists to hide and avoid exposure to the question "What's new?" While reading the scientific literature Paul Janssen took notes, often accompanied by chemical structures and diagrams, on small pieces of paper. These were collected by his secretary and when sufficient in number were edited into an internal newsletter that was circulated among the scientists.

The self-amplifying effect of Janssen's subtle and continuous stimuli produced a kind of resonance within the laboratory. It also tended to synchronize the activities of the various specialists towards common goals.

When a research project had matured sufficiently, it was time to start writing it up into an article. Usually Paul Janssen would then have a table cleared for him in the laboratory most involved in the project where he would spend a week or more writing and drawing diagrams. During all this time a collaborator was required to sit next to him and check and discuss all the minute details of writing a scientific publication. Often his role was restricted to that of a sounding board. A lot of time was spent in drawing diagrams by hand. It was Janssen's belief that this improved understanding of the data because of a feedback from the hand to the cognitive centers in the brain. In between, requests for analysis would be sent to the statistical department; drawings were ordered from the professional draftsmen and the secretarial staff had to type various versions of the manuscript. Needless to say that the routine work in the laboratory had to be taken care of as well, sometimes during the late hours of the evening. Several important articles came about this way, and two of them received the status of "citation classic".

The working day had no fixed duration. Janssen made a distinction between technical staff that were paid by the hour and scientists that were paid to accomplish a self-imposed task. In the early period it was not unusual for scientists to come to the laboratory on Saturdays. This was a moment where the going was more relaxed. It was the occasion for discussion of scientific matters of more general interest. Visits with scientists from abroad or with investigators that carried out studies with the compounds in the clinics were arranged on that day.

4. Metaphors used by Paul Janssen for his concept

4.1 The conductor and his orchestra
Paul Janssen most often likened his research to the functioning of an orchestra in which he assumed the role of conductor. The latter makes individual soloists play harmoniously together, while imposing his own esthetic interpretation of the work. Professional soloists require only a minimum of coaching and guidance, and work almost in symbiosis with the conductor, each deriving personal satisfaction and self-fulfillment from their respective roles.

Janssen had asked himself what would happen to the orchestra when the conductor was no longer present (Smith et al., 2004). From the beginning he was conscious of the great responsibility that he was assuming with respect to the (then mostly young) scientists who dedicated the best part of their active life to the success of his research enterprise. The affiliation with Johnson and Johnson in 1961, barely 8 years after the founding of the laboratory, provided Janssen with a kind of life insurance that would protect his collaborators if he were no longer around.

4.2 The fingers and the palm
Interdisciplinary pharmaceutical research involves many specialists, such as chemists, pharmacologists, statisticians, toxicologists and clinicians, all with different educational backgrounds and all following distinct scientific methodologies (Cech, 2004). Paul Janssen likened these various disciplines to the fingers of an outspread hand. He saw his own role as that of the palm, which interconnects the fingers and brings them closer together. He never pretended to be a master in the multiplicity of disciplines, although he was a leading expert in the field of medicinal chemistry and its clinical applications. Instead, he had an unlimited curiosity and eagerness to learn about all aspects of drug design, especially those fields in which he was initially less proficient.

4.3 The open mind
The idea of an open mind played a prominent role in research at the Janssen labs. While research has by necessity to proceed in an orderly and systematic way, serendipitous findings may be even more important than those produced by preconceived plans. “Chance favors the prepared mind” (Kubinyi, 1999). This was, for instance, how the Janssen antipsychotic compounds were discovered during the screening for analgesic compounds (Janssen, 1970; Healy, 1998).The open mind led to the rejection of intellectual authority, thus preventing researchers from being misled by inherited or ingrained misconceptions. Janssen constantly reminded his collaborators to assume as little as possible, read the literature critically and rely only on what could be understood. Hence his frequently asked question: “Can it be believed?” As an illustration, he strongly insisted on the use of distribution-free (also called non-parametric) statistics, whenever feasible, because he refused to assume without proof that data were normally distributed according to the “normal” (Gaussian) probability density function.

To Janssen the two main criteria for entering a field of research were medical need and available competence. As a researcher he did not like being told what to do by marketing and sales people. He firmly believed that by doing persistent, honest and useful research, with a bit of luck and a flair for opportunities, the success would predictably follow.

4.4 Care for the children

Janssen enjoyed the luxury of having a flow of highly active lead compounds, which he liked to refer to as “our children”, in each of his many fields of research. This was in part due to the stringent criteria used in the pharmacological screening, which tended to avoid false positives; those compounds that would have to be abandoned later on because of insufficient activity.

The parallel flow of lead compounds at Janssen meant that the selection of a compound for development was postponed to the last possible moment. As a result, there were many, almost too many, good drug candidates queuing up in late stages of development. Janssen, however, abhorred the slogan “Kill compounds early and fast”, popular today within drug companies. His reply was: “We do not kill our children”. However, as a formal system for setting priorities was lacking, the parallel flow often resulted in considerable strain upon supporting departments. In some cases later development of compounds had to be out-licensed to other companies.

The opposite of parallel flow is stage gating. In drug research, stage gating involves dividing research into a linear sequence of processes (called the pipeline), and then monitoring each stage by accounting metrics and decision making at the completion of each stage. Stage gating aims to avoid false negatives, those compounds that fail in later stages because of toxicity and side effects. It may cause rapid attrition of the number of candidates for late development, which then has to be compensated by in-licensing of compounds from other companies.

Parallel flow is generally more productive in breakthrough research, while stage gating is more appropriate for incremental research. In practice, a research director will have to strike a proper balance between the two extremes. Although Janssen’s approach was strongly in favor of parallel flow, radical and incremental innovations were inseparable. On the one hand, several breakthrough compounds were invented that became gold standards in their respective fields against which other compounds are still compared. Examples are fentanyl in analgesia, haloperidol in psychiatry, levamisole in parasitology, and miconazole in mycology. On the other hand, many follow-up compounds were designed with incremental improvements, such as in time of onset and duration of action, route of administration, safety profile and differentiation of medical indications.

5. Actuality of the concept

Evidently, Janssen's relationship with his employees was based on trust. Maximum freedom was given with minimum control and supervision. Paul Janssen's thesis was that good scientists do not need to be controlled, nor do they have to formally report and continuously justify themselves (Hughes, 1993). They are best left to do what they are good at and what they commit themselves to. From this perspective, motivation of scientists is based on self-realization while contributing to the common goal of producing novel and better medicines for important diseases.

Since non-hierarchical research allowed for a lot of freedom, the laboratory constantly changed direction as new opportunities appeared and new competences arrived in the lab. When prospecting for candidates, the question was not whether they would fit into the existing research organization, but rather whether the research could accommodate their competences. The arrival of parasitologists, mycologists, pharmacologists and toxicologists from the former Belgian Congo, after the declaration of its independence in 1960, is a case in point.

Janssen directed his researchers according to Theory Y of McGregor, which holds that people are in general trustworthy, eager to work and aspiring to self-fulfillment, and hence should be given maximum freedom. The opposite view is Theory X, which holds that people are in general unreliable, lazy and negligent, and hence must be controlled in all circumstances (McGregor, 1960). In practice a director will adopt an optimal mix of Theories Y and X, but Janssen's concept was very outspokenly Theory Y. One drawback of this position was that a break of confidence between Paul Janssen and a researcher was always beyond repair. In that case, the only way out was "out".

Janssen's concept of organizing around competent people and critical questioning has proven its value by creating one of the most successful research environments in the field of medicinal chemistry. Yet, the validity of his concept is nowadays challenged. The three most frequently heard objections are that (1) the concept is no longer applicable in an increasingly difficult research environment, (2) the concept only works well with small groups of researchers, and (3) the concept requires the presence of a charismatic leader. We reflect briefly on each of these objections.

5.1 First objection: The concept is no longer applicable in an increasingly difficult research environment ("All the low-hanging fruit has been picked").
First, it must be remembered that the early years of the Janssen laboratory were all but easy. Initially, there was much disbelief in his project from the outside; resources were scarce; qualified scientists were not easily attracted by a small-scale and risk taking pharmaceutical research enterprise. The thalidomide crisis in the sixties had produced a radical increase in the demands for toxicological testing from the regulatory agencies. Janssen handled the situation by focusing

on medical need rather than on market potential. Several compounds were developed as so-called “service products” for the medical profession, which generated little or no profit, but created goodwill and reinforced the image of a research-driven company. Meetings with regulatory agencies were often handled by a single scientist. In line with his character, Janssen often did things the other way around from normal practice, and with success.

Over the past decade investments for development of new drugs have increased whilst the number of new introductions on the market has decreased, in part due to more stringent regulatory requirements. This evolution has resulted in risk aversion within the industry and its preference for blockbuster products, i.e. drugs that are used by many people for a prolonged period of time. This, in turn, is bound to produce increased concerns and alertness from the regulatory agencies and the medical profession. The result is a demand for even more tests and studies, which once more add to the cost and time of development of a new drug. Paul Janssen, among others, warned that this vicious spiral may ultimately lead to the downfall of the pharmaceutical industry, much to the detriment of the health and well-being of the world (Janssen, 1981; Brown 2003).

The classical paradigm of drug design, which was fervently advocated by Paul Janssen, starts from clinical observations, reliable animal models and medicinal chemistry. The modern paradigm focuses on the discovery of genes that can be expressed into new molecular targets for which ligands can then be designed, in the hope that these will eventually reach the clinic as medicines. Janssen often warned that there are many assumptions in this approach that remain untested, and that many years will be required before it lives up to its promises. In his opinion, the classical paradigm had been rejected too soon. It would be more prudent and rewarding to adopt a smooth transition between the classical and modern paradigms of drug design (Horrobin, 2003; Williams, 2004). Only by taking this approach will it be clear “how much low-hanging fruit is still waiting to be picked”.

5.2 Second objection 2: The concept only works well with small groups of researchers.

Using Janssen’s own metaphor, the reflection implies that playing with a small Jazz combo is easier than conducting a large orchestra. Nevertheless, Janssen maintained his concept of orchestrating research even when the laboratory in its hay day employed several hundred scientists and technicians. As research was organized around competent people, the latter tended to imitate the example set by Dr. Janssen and they implemented his concept in their own units. Furthermore, supportive functions, such as statistics, patents, documentation, secretarial work and so on were kept centralized, so as to free researchers to do their own “management by walking around”. Janssen acted as a role model and a source of inspiration for young scientists as well as for the old hands. His role as conductor was to keep all the members of his orchestra in tune with each other, by encouraging resonance and promoting synchrony.

A problem with organizations is that it is often much harder to do away with layers of command than to add to them. Human nature, after all, finds it difficult to give up control and power, even in cases when it serves the interest of the community (Brown, 2003).

5.3 Third objection: The concept requires the presence of a charismatic leader. It is said to be inevitable that when a charismatic leader, such as Dr. Paul Janssen, disappears his place is taken by a more formal organization. It is also not unusual for the legacy of the founder of an important undertaking to be neglected or even rejected after his passing away. This may be due to a generational conflict or the result of struggles for succession between the different visions among its heirs. There are examples, however, of great political, academic and industrial enterprises that have survived several generations and have produced competent and inspiring leaders as needed. Apart from their organizational structure, which may go through cyclic changes, these enterprises invariably possess and nurture a testament, constitution, manifesto, charter or credo. This serves as a kind of beacon, touchstone and reminder of the founding concept. Respect for tradition and reflection on the cultural and spiritual heritage will eventually produce the leadership that is needed to tackle the problems facing the industry today.

There is much emphasis nowadays on emotional intelligence as a prerequisite for natural leadership (Goleman et al. 2001; Vojak et al., 2006). Paul Janssen's charismatic leadership stemmed from emotional understanding of people, be it his collaborators, patients, physicians or the public at large, rather than a concern for processes, committees, slogans, titles or even buildings. This attitude does not require special education or training, but derives from a genuine interest and concern for people.

6. Conclusion

At a meeting of the Medicines Research Association in London in 2003, the year of his sudden death, Dr. Paul Janssen delivered a talk based on a paper published by him more than 20 years earlier (Janssen, 1981). In this paper he had listed the factors that he believed fostered productive medicinal research. These included teamwork, interest in basic science, awareness of medical needs and intellectual freedom. He also pointed out the factors that smothered productive research, such as excessive bureaucratic control, hierarchical reporting structures and decision-making by committees (Janssen, 1980).

Paul Janssen's concept of "organizing around competent people" and "continuous critical questioning" was inspired by common sense, typical for the people among whom he grew up. It was also driven by his concern for human beings, which stemmed from his medical training and family environment. Janssen was convinced that at the end of the day it is the people that make the

difference. He respected courage as much as intelligence and experience. His concept resulted in people showing courage in the face of seemingly insurmountable difficulties and excelling beyond limits that they themselves had thought unattainable. Failure never entered the minds of those who performed by this concept. Success followed from honest research, perseverance and a bit of luck. Given these conditions success becomes a habit.

Our intention here has been to present from personal experience a flavor of what it was like to perform research in a stimulating and productive environment. The formal description of Paul Janssen's concept of organizing research is left to others more schooled in this matter.

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