

Drug Design with Dr. Paul Janssen



**Narrated by Paul Lewi,
former collaborator of Dr. Paul Janssen**

In this monograph I would like to tell about the research and the personality of Dr. Paul Janssen, the founder of Janssen Pharmaceutica.

Like several of my former colleagues, I have worked for more than forty years with Dr. Paul Janssen or Dr. Paul, as he was always called by his collaborators with much respect and affection.

Our first research building was rather small. It comprised a laboratory for chemistry and pharmacology. There wasn't much more. After five decades the company has expanded to become a large village with more than four thousand people.

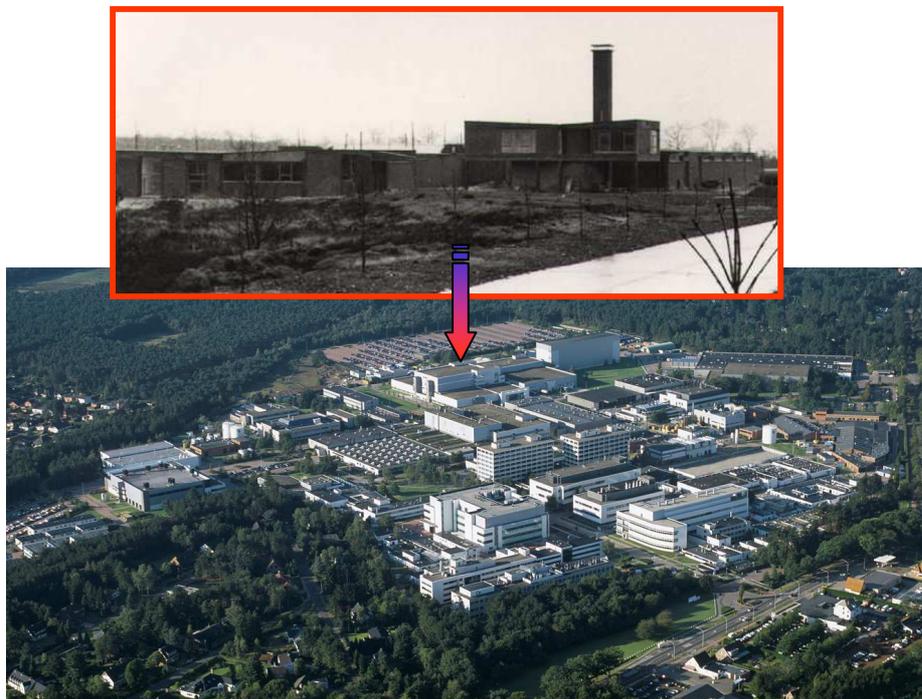


Fig.1 The Janssen laboratory in Beerse at the start in 1957 and more recently.

When I first met Dr. Paul he had just finished medical school. Forty years later Paul Janssen had become the most productive drug inventor of all time.

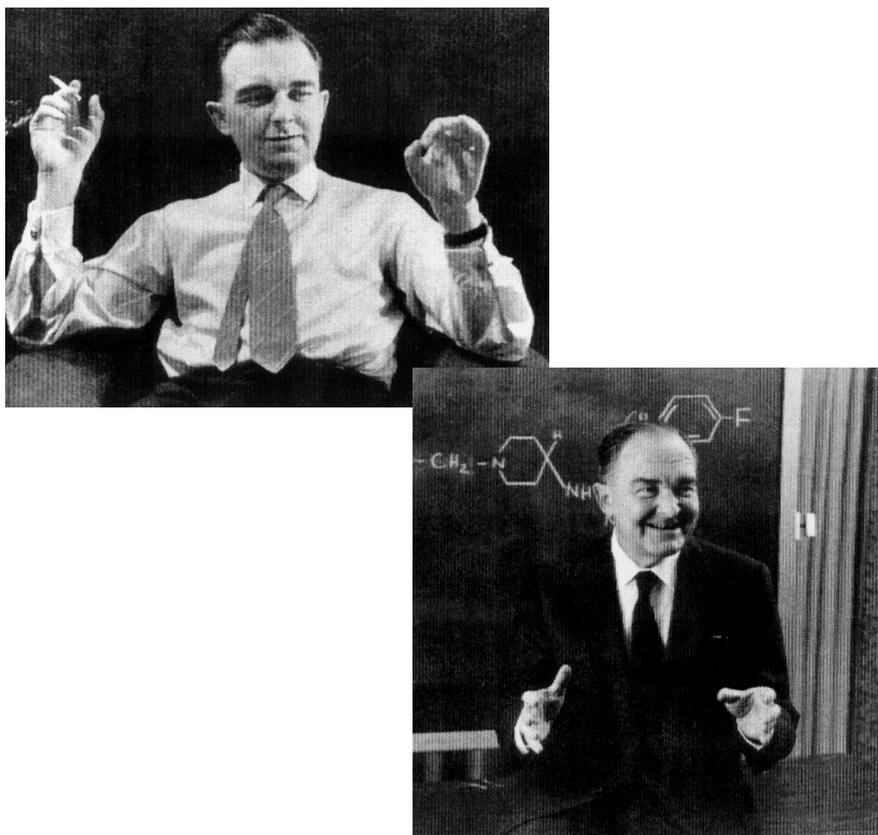


Fig.2 Dr. Paul in the early days of the laboratory and at the peak of his research activities.

You may have the impression from the two photographs that Dr. Paul talked often about fishing. It looks as if in the beginning he wanted to catch a very big fish. A very important medicine, of course. For many years his fishing went very well, although a few fishes were a little bit smaller than he had hoped. Nevertheless he built the most famous medicinal research laboratory of the world.

Success came rapidly from the start. Many people then visited us. But the visitors did not understand where our success came from. Our laboratory was small. Our equipment was mostly made in our own workshop. Most of our scientists did not have an academic degree. So the visitors asked where the success of Janssen came from. I think that the secret of Janssen's success lied in his personality. I will explain this in more detail.

Paul Janssen's ancestors were farmers. Our farmers are strong-headed and tenacious. They say: "You must not believe what people say or write". They also say: "Sometimes it is better to do things differently". Perhaps it is the same in many countries. Paul Janssen had kept the mentality of the farmers.

Paul Janssen's great dream was to invent many synthetic medicines and determine their pharmacological properties by simple tests. In those years everybody thought that this was totally impossible. Luckily, Janssen's father had founded a small pharmaceutical company. It produced classical medicines like vitamins and organ extracts. The father wanted his son to work in his factory. But Paul Janssen wanted to realize his own plan. Finally his father gave him a kind of garage in his factory and four persons to assist him.

After one year Janssen and his team had synthesized five hundred new chemical compounds. It is remarkable that seven of these five hundred

compounds became a medicine. Today this would no longer be possible.

Compound number seventy nine (isopropamide iodide) would have been called a “blockbuster” today. It was prescribed against stomach pain and gastric ulcers. You must understand that this was shortly after the Second World War. People began to eat a lot of food again. They also suffered from its side effects, namely gastric pain and ulcers. This product immediately became a big success and the laboratory expanded rapidly thereafter.

As a consequence of the expansion Paul Janssen had to organize his laboratory. He observed that large pharmaceutical companies had organized their research in a vertical way. There were many managers in the offices and only relatively few people in the laboratories.

Janssen, by contrast, conceived of a horizontal organization. He organized his research around competent scientists. I will explain this concept with an example.

When our colony became independent in the early sixties, many Belgians returned from Africa. They had worked for decades in the sanitary and veterinary services of the colony. Paul Janssen said to them: “Come to work here, we have a lot to do”.

One of these colonials had a passion, almost obsession, with parasites. Janssen had never thought about antiparasitic compounds. He asked the marketing specialists for advice. They said that there

was no profitable market for antiparasitic medicines. They were right. At that time there were almost no active and safe antiparasitic compounds. Hence the market for them was very small.

But Janssen was impressed by the man's experience and knowledge. He offered the parasitologist a small laboratory. Imagine a table, two chairs, a microscope and some test tubes. A young girl was also assigned to assist him with his experiments. These had to be as simple as possible, because Dr. Janssen wanted to learn about parasitology in order to understand what the parasitologist was doing.

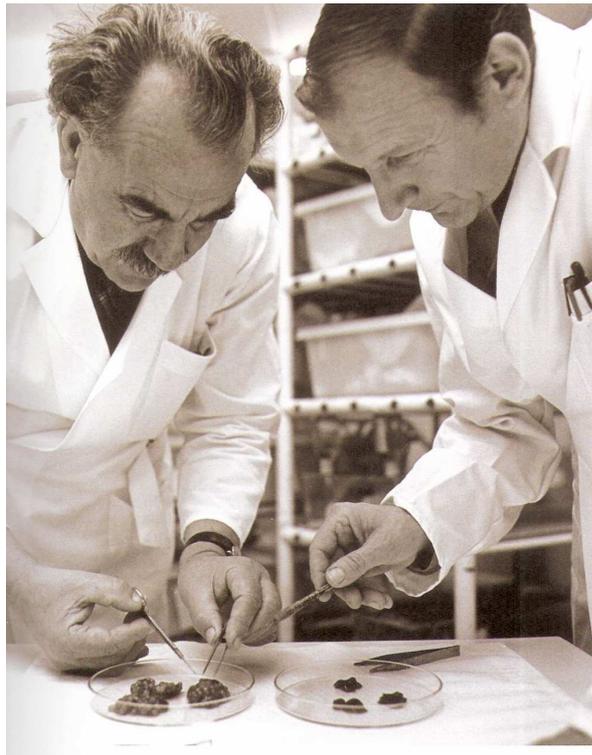


Fig.3 Parasitologists at work at Janssen after their return from Africa.

After one year this small team produced tetramisole and levamisole, the first synthetic, highly active and very safe antiparasitic compounds. During the following years the laboratory invented eight other antiparasitic medicines, among which mebendazole.

Another scientist that came to us from the colonies was a mycologist with a passion for fungi, yeasts and molds. The same scenario evolved as with the parasitologist. Dr. Paul asked advice from the marketing specialists. They told him that the antifungal market was saturated. Of course there were already some antifungal products available at that time, such as griseofulvin, amphotericin B and nystatin. But these products were not without serious side effects.

Dr. Janssen, however, decided to give the mycologist a chance. A small laboratory was arranged for him. Imagine a table, some chairs, test tubes, a microscope and a girl to help him with his experiments. These must also be as simple as possible, as Dr. Paul wanted to learn and understand what the mycologist was doing.



Fig.4 Mycologist at work at Janssen after his return from Africa.

After one year and a half of hard work, this laboratory produced the first synthetic, highly active and safe antifungal compound, which was miconazole. Thereafter twelve other antifungal products were brought to the market, the last of which being itraconazole.

The same happened with many other scientists that came to join us. Often people were hired because of their special talents without there being a specific vacancy for them. Janssen said that the laboratory must adapt to the abilities of the people who were there or came to us, and not vice versa. The laboratory evolved more like an organism than an established organization.

Janssen was not a person who used to give orders. Instead he asked his assistants to come up with interesting ideas and plans. He continuously asked: "What's new?". He did not exercise control from his office. He was most of the time in the laboratories. Nowadays directors are not often seen in the laboratories. They have to attend many meetings and need to travel frequently.

Janssen made every day a round through the laboratories. When he entered a laboratory his first question was: "What's new?". His collaborators had usually prepared their answer. When Janssen went out to visit the next laboratory, someone would take a spoon and tap on the tubes of the central heating. This was a warning sign for those working farther in the corridors. It meant: "Take care! Dr. Paul is coming! Don't get caught with nothing new to tell!". It

happened that peopled saved some extra news for the days when there was not much news to tell.



Figs.5 and 6 *Dr. Janssen (in the middle at left) discussing a new synthetic molecule with the chemists and listening to a proposal for a new test from the pharmacologists.*

Janssen has never forbidden to go ahead with a well thought out plan. But, the one who committed himself to a new project had to be prepared to fight for it when difficulties arose. Janssen admired courage more than intelligence. He said that courage is shown when everything seems to be lost and one must fight with his back against the wall.

When asked what his function was at the research laboratory, Janssen invariably answered: "I am the conductor of an orchestra".

Paul Janssen was also an excellent chemist. He had observed early on that the chemical motif “phenylpropylamine” is present in many biologically active compounds. You can see this chemical motif in morphine, codeine, pethidine and many other compounds.

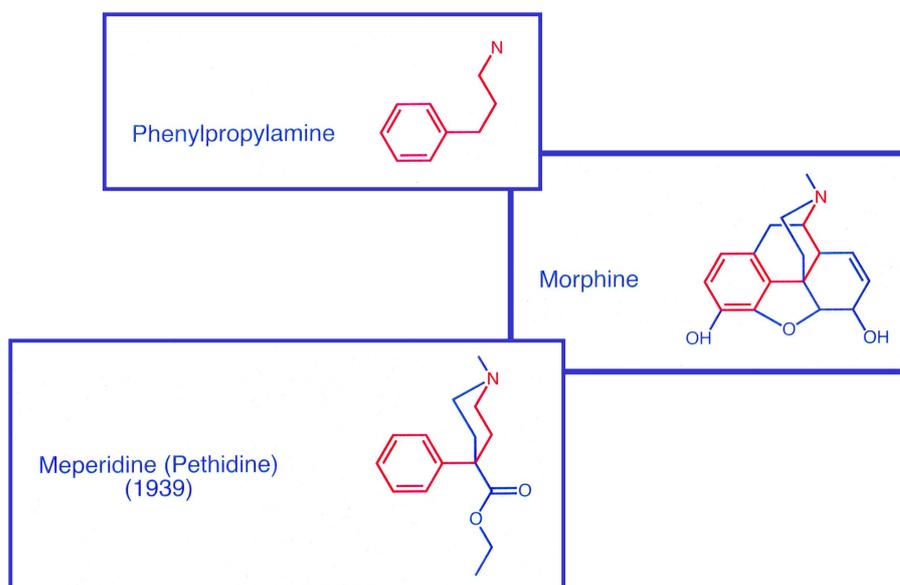


Fig.7 Phenylpropylamine.

The motif “phenylpropylamine” is composed of a phenyl ring, an amine function, which is represented by a nitrogen atom, and a chain of three carbon atoms linking the two together.

Janssen knew that small chemical variations can cause large pharmacological and clinical differences. Hence, he started his research by making variations on the “phenylpropylamine” motif. Initially it produced antispasmodics, antidiarrhoeals and potent analgesics such as fentanyl.

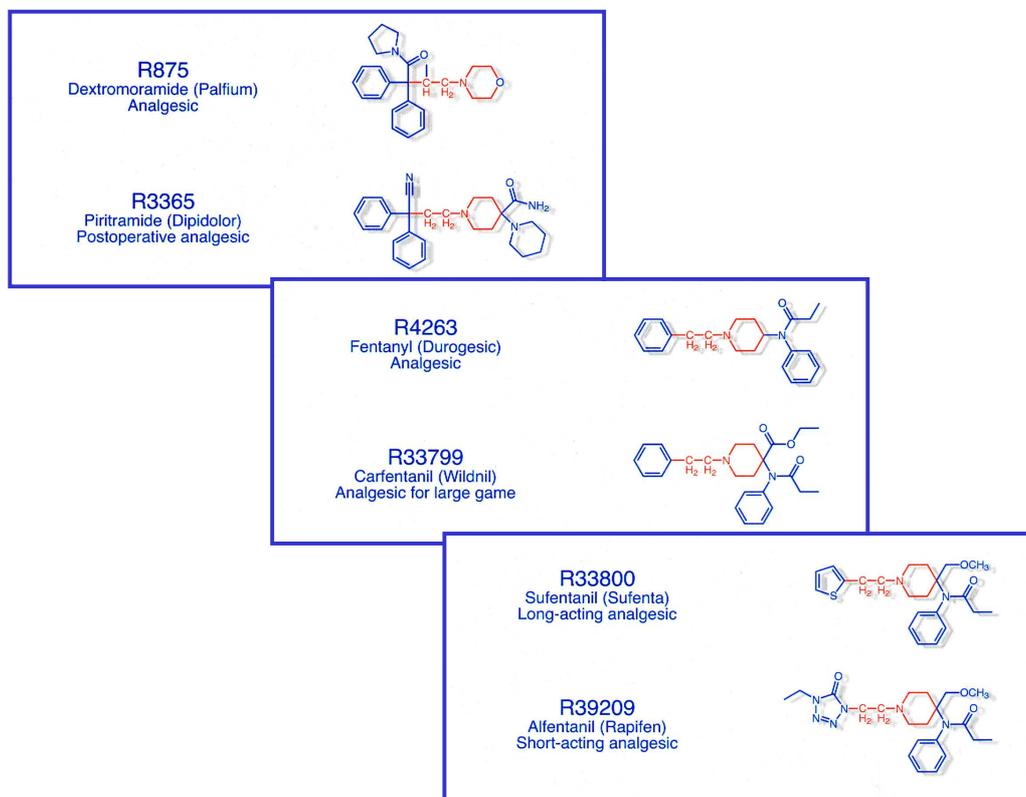


Fig.8 Selected analgesic compounds from Janssen Research.

All our compounds were routinely tested for analgesic activity. A simple test for central analgesia consisted of a hot plate, such as is used to keep coffee warm. If a mouse is placed on the hot plate it will lick its paws to remove the heat. With central analgesics, the mice are very agitated and try to escape from the plate.



Fig.9 Hot plate test for analgesic effect.

The picture shows how the hot plate test is used to measure the analgesic activity of a compound in mice. A stopwatch is used to measure the time that elapsed before the animal starts licking its paws.

But with one particular new compound the reaction of the mice was the opposite. It was as if they were tranquillized. The mice did not move at all. They simply sat there on the plate and did not seem to care about the heat. Clearly the new compound should be used in psychiatry rather than in anesthesia. Therefore Janssen contacted a famous

psychiatrist and a sample of the compound was sent to his psychiatric clinic.

Shortly thereafter, something very spectacular happened in the psychiatric clinic. A young person was brought in the clinic with a severe psychosis. He was very aggressive and had severe hallucinations. The psychiatrist remembered the sample that Janssen had sent. The compound had already been tested for safety on rats and dogs. So it was decided to inject a few milligrams of it. The antipsychotic result of the new compound was unexpectedly strong and rapid.

This was the first clinical study of haloperidol in humans. It involved only one person. But the result was highly convincing. After only one year of clinical studies haloperidol was approved and made available to the patients.

Haloperidol became rapidly a great success, first in Europe and then in the US and all over the world. It had a dramatic impact on the duration of hospitalization of psychiatric patients and their treatment. Therefore it was listed as an essential medicine by the World Health Organization. It also became the golden standard against which other antipsychotics are compared.

Notwithstanding this success Janssen wanted to synthesize and explore many derivatives of haloperidol, bearing in mind that sometimes small changes produce large pharmacological and clinical effects. What was lacking, however, was a specific test in animals for measuring antipsychotic effect of

experimental compounds. By chance, Paul Janssen met with the physician who accompanied the Belgian cyclists. He remarked that cyclists who took amphetamine for improving their performance showed typical phenomena of psychosis. They often had to be stopped by force and drawn from their bicycle after they had finished the contest. They also exhibited stereotyped behavior in their gestures and speaking.

The pharmacologists at Janssen soon found that rats which had been pretreated with amphetamine showed cataleptic and stereotyped behavior, such as rigid postures, continuous gnawing and agitated movements. These phenomena could be readily inhibited by haloperidol.

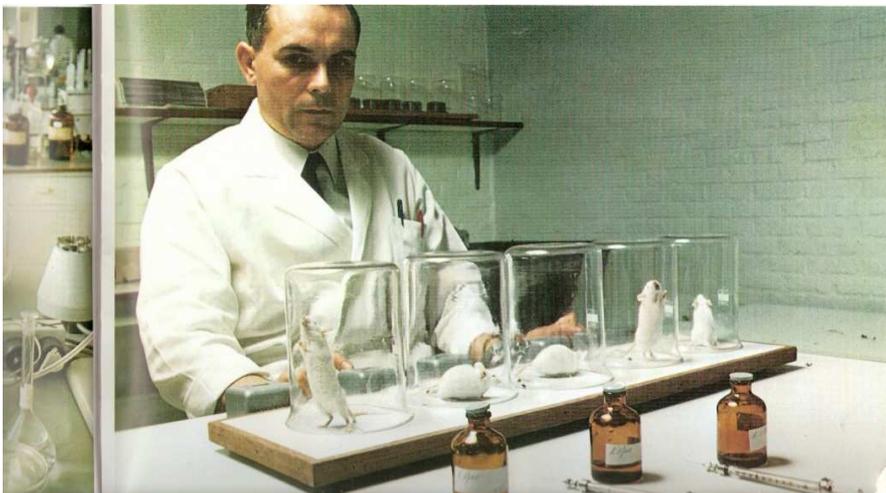


Fig.10 *Observation of behavior of animals by a laboratory technician.*

This way, a highly sensitive and reproducible animal model for antipsychotic activity became available. It greatly stimulated antipsychotic research at Janssen

and led to interesting new compounds. One of the early derivatives of haloperidol was pipamperone which showed a combined inhibitory effect of the effects of amphetamine and tryptamine. Nowadays this compound would have been called an atypical antipsychotic. Now we know that atypical antipsychotics inhibit at the same time dopamine and serotonin receptors. But in the early sixties the clinical importance of this mixed effect was not fully appreciated.

In total the laboratory invented seventeen antipsychotic medicines over a period of forty years. The latest of these are the atypical antipsychotics risperidone and its close analogue paliperidone.

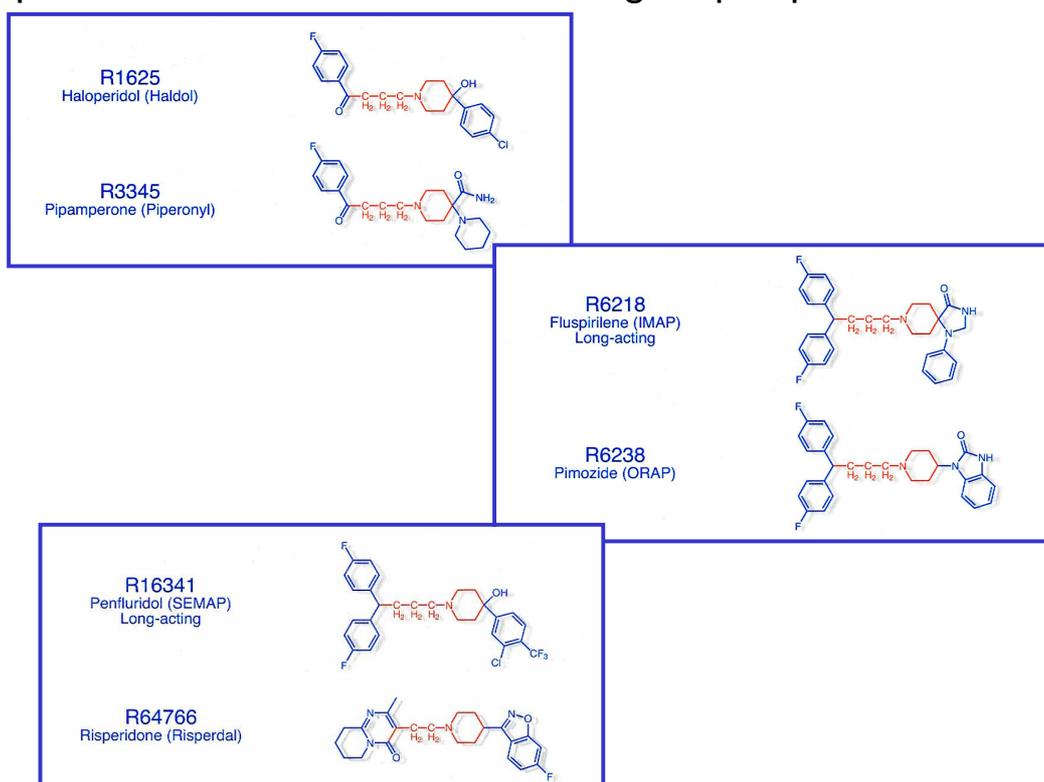


Fig. 11 Selected antipsychotic compounds from Janssen Research.

Paliperidone differs only with one hydroxyl group from risperidone. Nevertheless the pharmacodynamic properties of the two products are very different. Small chemical changes often produce large biological differences. Think of morphine and codeine, which only differ by one methyl group. Risperidone and paliperidone are really two different products.

Janssen wanted to do research until the end of his life. After his retirement he asked me to help him set up a Center for Molecular Design with funding from Janssen Pharmaceutica. The center was located in a country house in Vosselaar at a distance of three kilometers from the central site in Beerse. It had only a small scientific and technical staff. There were no laboratories.



Fig.12 *The Center for Molecular Design (1995 – 2005). The photograph shows the author (at left) and one of his former colleagues.*

There were also no animals, except for the mice in the cellar and a cat in the garden. But, it had a supercomputer to do drug design by molecular modeling.



Fig.13 *Dr. Janssen (at right) discussing a new design for an anti-HIV compound with molecular modelers.*

The picture shows Dr. Janssen in the modeling room at the Center for Molecular Design. At that moment the scientists were designing new compounds against HIV, the virus that causes AIDS. Dr. Paul had just asked the molecular modelers whether they had found “anything new” that day.

The center focused on the design of anti-HIV compounds. At that time the market for anti-HIV compounds did not look attractive. But Dr. Janssen always maintained that research must come before business. He always emphasized that one must do what is medically important and for which one has the

necessary competence. Of course, AIDS is a terrible disease which makes millions of victims every year, mostly in regions where medical care and access to medicines is not readily available. Our experience in the field of HIV was already considerable as we we had discovered compounds that strongly inhibited the enzyme HIV-reverse transcriptase. The latter transcribes the viral genome from RNA into DNA such that it can be integrated into the genome of the human host cell. This is an essential step in the reproduction of the virus.

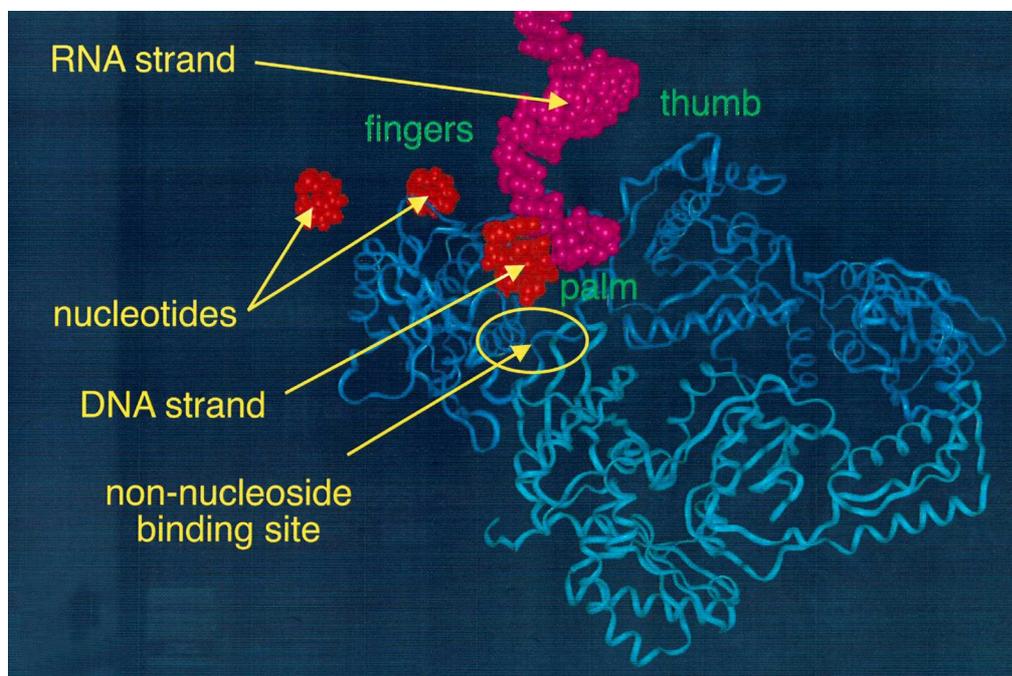


Fig.14 HIV-reverse transcriptase with viral RNA and transcribed DNA strands.

The figure represents the enzyme HIV-reverse transcriptase. Transcription of RNA into DNA takes place in the upper part of the enzyme. This part is composed of three domains called “thumb”, “palm” and “fingers” by analogy with the form of a hand. A viral string of RNA is taken between “thumb” and “fingers”

and squeezed forward, nucleotide by nucleotide. At each step, incoming nucleotides are chained together and build a complementary string of DNA which will be integrated later on into the human genome. This transcription process can be likened to the assembly of a zipper.

The first anti-HIV drug AZT (or zidovudine) yields a false nucleotide which can still attach to a newly formed string of DNA, but does not allow further attachments to be made. For this reason AZT is referred to as a chain terminator.

Several years ago Janssen and collaborators had discovered a small cavity in the enzyme immediately below the transcription site. Small molecules can be designed that fit into this pocket and bind strongly to it. This blocks the movement of “thumb” and “fingers”, which in turn stops the transcription process and finally the reproduction of the virus.

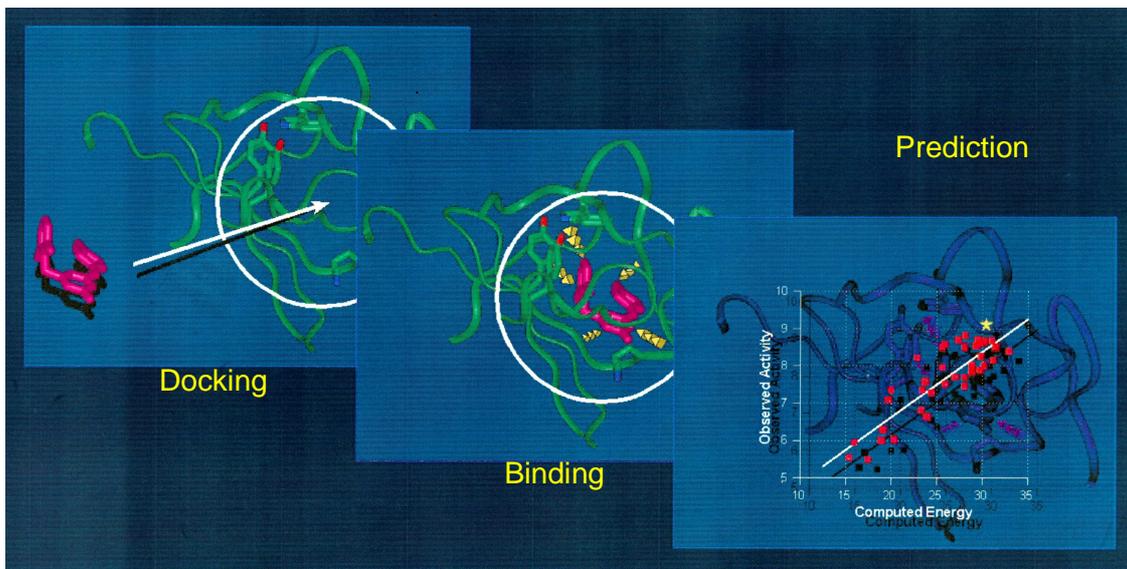


Fig.15 *The three steps in Molecular Modeling.*

At the Center for Molecular Design the binding of molecules to a target protein was studied by means of molecular modeling on a supercomputer. The process basically involves three steps.

First an attempt is made to “dock” the molecule into the binding pocket of the protein. If the molecule is too large, it will not enter. If it is too small it will not make useful contacts with the wall of the pocket.

The second step is the most difficult one. It involves the calculation of the binding energy that is released when a small molecule attaches to the target protein. This is a very complicated problem of quantum chemistry. The greater the energy that is released the more stable is the binding. By analogy, the more comfortable a chair is, the more difficult it is to get out of it.

In a third step, once the binding energy has been determined, statistical techniques are applied to predict the antiviral activity.

In fact, molecular modeling of the interactions between a small molecule and a protein is somewhat more complicated than was explained above.

One must imagine that initially the small molecule swims around inside the infected cell. It has a lot of freedom to vibrate, move and rotate. It does not stay for a long time at the same place and in the same position. Suddenly it sees itself positioned before the entrance of the binding pocket of the protein. It must now decide either to enter or to continue its journey outside. If it decides to enter it will gain stability by

binding to the wall of the binding pocket. But at the same time it will lose most of its freedom of vibration, movement and rotation.

Therefore, the molecule must evaluate the balance between the change in stability and the change in freedom that will result from its decision. If the balance is favorable it will enter and stay inside the binding pocket for some time and thus inhibit the function of the protein.

The balance between freedom and stability is a universal phenomenon. In thermodynamics it is known as the trade-off between entropy and enthalpy. Freedom can be expressed in terms of entropy. Stability can be quantified as enthalpy, which is the heat exchanged with the environment.

A couple that considers marriage often must evaluate the possible gain in stability and loss of freedom that will follow from their living together.

Tightly managed organizations may provide very stable employment but provide little opportunity for initiative. These can be termed as enthalpic organizations. Janssen provided much freedom to its collaborators. But his organization could change from one day to another, depending on the course of research and the advent of new people. It is to be regarded as a typically entropic organization.

Very soon a new class of anti-HIV compounds was discovered on the computer screens of the Center for Molecular Design. Unlike AZT these compounds are not nucleosides. Therefore they are called non-

nucleoside inhibitors of HIV-reverse transcriptase. One of these, etravirine, has been approved by the FDA for treatment of HIV-infected patients.

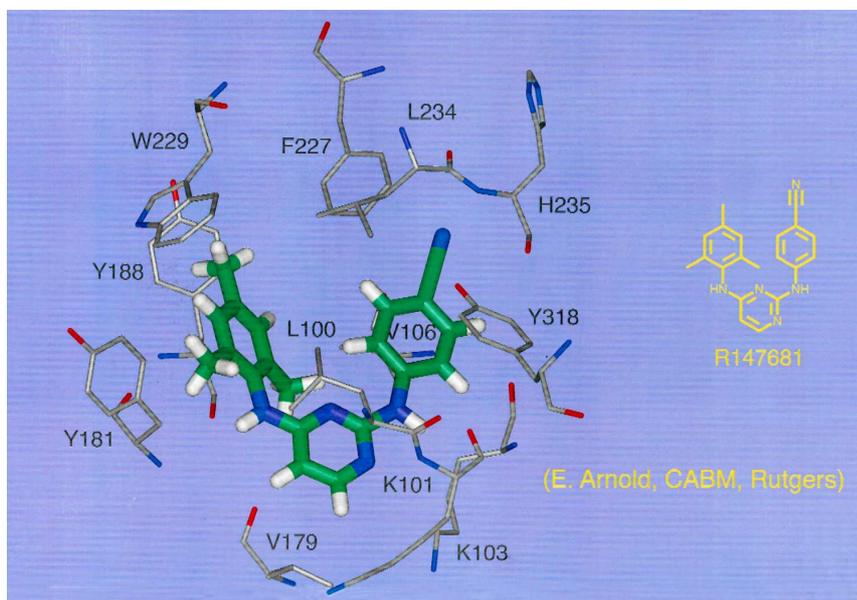


Fig.16 Binding site of HIV-reverse transcriptase and a designed anti-HIV compound bound within it.

This figure shows the result of molecular modeling on the inhibition of reverse transcriptase of HIV, as it appeared on the screens of the supercomputer. Reverse transcriptase is an enzyme that is essential for the reproduction of HIV. For convenience, the picture shows only a few characteristic amino acids that line the wall of the binding site.

The designed small molecule at the center of the figure fits tightly into the binding pocket of the protein. It also makes strong electronic interactions with the amino acids that line the wall of the pocket. It is the prototype of the new class of designed anti-HIV compounds.

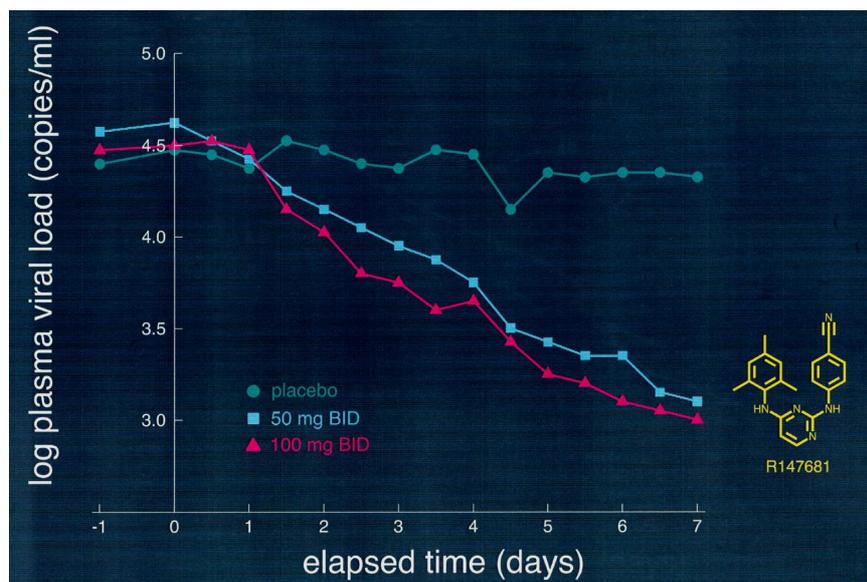


Fig.17 *Result of a clinical study of a designed anti-HIV compound.*

This diagram shows the result of a clinical study of the designed compound on HIV-infected patients.

The axes represent the number of viral particles in plasma, also called viral load, as a function of days of treatment. Viral load is expressed here logarithmically such that the number three represents thousand viral particles per milliliter of plasma; the number four represents ten thousand particles per milliliter of plasma and so on.

It can be readily seen that the control group does not change over time, as would be expected. But the viral load in the two treatment groups decreases exponentially. After one week of treatment the virus became undetectable in the blood of the patients. This offers an encouraging perspective for the treatment and prevention of HIV, especially in regions where resources are scarce.

Work at the Center for Molecular Design under the guidance of Paul Janssen was very productive and at the same time relaxed. Often, when the weather allowed, scientific discussions were held in the large garden of the Center.



Fig. 18 *Dr. Paul (seated in the center) and the author (seated at left) discussing with visiting scientists from abroad.*

Dr. Janssen was also greatly interested in history, literature and music. He could speak fluently in several languages and played the piano well.



Fig.19 Dr. Paul playing the piano.

Unfortunately, Dr. Paul Janssen died suddenly at the age of seventy seven, while attending a scientific conference in Rome. As he had always wished, he had dedicated himself to science until the last minute of his life.

His contribution to mankind is the invention of eighty medicines. He was the most prolific inventor of medicines of all time and is regarded as the Thomas Edison of medicinal chemistry. He did not live long enough to receive the Nobel Prize, for which he was nominated for several years.

But, his concept of research is still alive. It can be summarized by his favorite question: "What's new?"

Paul J. Lewi, PhD, Eng, BSc
Turnhout (Belgium), April 2008

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Figures 14, 15 and 16 are based on data provided or published by Prof. Dr. Eddy Arnold (CABM, Rutgers University, New Jersey).

Figure 17 is based on data made public by B. Gruzdev et al. (Abstract 13, CROI, Chicago, 2001).

Figure 18 has been kindly provided by Mrs. Dora Janssen.

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**List of Janssen product names mentioned in the monograph
(Generic name – Brand name)**

Isopropamide iodide – Priamide
Tetramisole – Nemicide
Levamisole – Ergamisol, Ripercol
Mebendazole – Vermox
Miconazole – Daktarin
Itraconazole – Sporanox, Sempera
Dextromoramide – Palfium
Piritramide – Dipidolor
Fentanyl - Fentanyl, Durogesic
Carfentanil – Wildnil
Sufentanil – Sufenta
Alfentanil – Rapifen
Haloperidol - Haldol
Pipamperone - Piperonyl, Dipiperon
Fluspirilene – IMAP
Pimozide – ORAP
Penfluridol – SEMAP
Risperidone- Risperdal
Paliperidone- Invega
Etravirine – Intelence