Experiments and experiences

Juninger, H.E.

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Prof. Dr dr.h.c. H. E. Junginger

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Mijnheer de rector magnificus,
Dear friends and colleagues, ladies and gentlemen.

To say farewell means to remember. For this reason I will dedicate this farewell lecture not primarily to the latest developments of my research discipline but to talk about my experiments and experiences as a Dutch professor with a German passport over the last 23 years at Leiden University and in The Netherlands. Not to talk primarily about research in the field of drug delivery is due to the fact that many of you have attended my farewell symposium during the last two days where excellent speakers have given you the state of the art of this area. However, I will give you my views about the future of drug therapy and drug delivery later on in this lecture.
Because many of you are not so familiar with the Dutch language, I got the permission from the rector magnificus to give this lecture in the English language. When I invited my old Dutch language teacher, professor Cor Soeteman (and here I can really say old, because he is with his 91 years certainly the oldest guest of today) to this symposium and informed him that I will give my farewell lecture in English, he immediately replied that this is excellent because in this case he has not to correct my Dutch manuscript. You may think that this is not a real compliment about my knowledge of the Dutch language even after 23 years. I only can tell you that the Dutch language is a very difficult one. Just recently there was in the radio news a comment that around 75% of the native Dutchmen have problems to use their own language correctly. Anyhow, he was my Dutch language teacher and I visited him in the beginning of my stay in Leiden every week with my prepared lessons. I learned not only Dutch but also I was informed about the history and traditions of Leiden University at the highest level, because professor Soeteman was also rector magnificus of Leiden University in 1970/71. Pay unit was a bottle of (preferentially German) white wine. At that time it was a little problem to get all the bottles into The Netherlands, because the European Union was still far from being reality and hence the import of wine was restricted to 2 liters per person and checks at the border have been routinely performed.
Although I have never been a real champion in languages I felt that I made some progress relatively quickly. Arriving during the first years from one of my many travels at Leiden railway station and taking a taxi back home or to the department, the taxi drivers supposed after some conversation that I am not a Dutch. In the very beginning they thought I am Belgian, then they moved me over the border to the Netherlands and thought I would come from Limburg and later even from Brabant. To my personal regret, I was never recognized as a Leiden citizen. In general, the real breakthrough in commanding a language is, when you go to the market, give your orderings in Dutch and the reply is not German any more but really in Dutch. Then you made it! The same holds if you pick up the phone and you immediately understand the message that is given to you phonetically. And even better if you have not to ask your neighbors anymore when your young children come home with words

which you doubt that they belong to the vocabulary they should use. But in summary, learning the Dutch language so quickly gave me a lot of credit of my colleagues.

Just some remarks about Leiden University traditions: when you are appointed as professor here in Leiden you have to give your inaugural lecture. In former times you did not get paid by the university before you did not have done so, but this rule fortunately has been abolished due to the long waiting list to get a date. For instance, I gave my inaugural lecture 14 months after being appointed. For your inaugural lecture you have to wear under your new gown, called toga, a tail and it is basically the only chance as normal professor to get admitted to talk from the higher pulpit behind me. For the farewell lecture you have to use the lower pulpit and you can decide either to wear a normal suit or as I did to again wear the toga together with my colleagues from Leiden and also from other universities. I must admit that I always was very proud to wear my Leiden toga on many occasions.
Originally, I was appointed as professor for pharmaceutical technology and dispensing, because at that time Leiden University still had a school of pharmacy. It was also expected that I would continue the research in tabletting as has been performed by my predecessor, professor Ko Polderman. He is also here today and it is certainly a real privilege to welcome him here today. But back to the experiments: two very simple tabletting experiments with magnesium stearate and lactose powders, one mixed for 1 min and the other milled for 1 hour showed me, that I could better change to another research area, because both compression experiments showed the same force-displacement curves. But the physical results were quite different: whereas the gently mixed powder resulted in a hard tablet, the "deadly mixed one" remained more or less a powder or very soft tablet when ejected from the die. To my opinion – even having one of the best equipped and calibrated tabletting machines at my hands in my new department – the experiments clearly showed the limitations of force-displacement measurements in powder compaction at that time.
Hence after these crucial experimental results I decided to start in Leiden with the research area of colloidal structures of ointments and creams on which I had already worked in Braunschweig as well together with professor Claus Führer. Also the first Ph.D. theses done in Leiden covered this area which later has been greatly extended by the late Harry Boddé. Currently, Joke Bouwstra is focusing more and more also on the biophysics of the skin and modern transdermal drug delivery. Most of the money I got after my appointment to establish my research was used to buy a Kratky camera with a position sensitive detector and the Balzers freeze etching apparatus. Whereas the first is replaced today by synchroton techniques, the latter one is still in use.
With my German scientific background I was really surprised about the Dutch research culture, open and international with all publications in the English language and a strong interest in mutual collaboration. I always found and still feel this situation so unique that no offer could get me back to Germany or to another country. And this open research culture certainly gives the Dutch universities an advantageous

basis to continue with superior research especially in times when the money is scarce. As everybody knows research in the life of a professor is one thing, but the rest is spent on meetings. The Dutch magic word for this is "vergadering" and sometimes (at least in the beginning) I got the impression that 50% of the academic staff were attending a vergadering, whereas the other 50% could work. This statement especially holds when you consider that many committees were busy to work out new strategies, with the other 50% trying to implement these plans.
The 3rd task of a professor is to teach. It started with some difficulties for me when giving my lectures in the Dutch language for the first time. On many occasions it resulted in a lot of hilarity on the students' side. Imagine you try to explain something and suddenly the students start to laugh and you don't know why! Nevertheless, the relationship with the students was always good and we had the gentleman's agreement that I will try to teach them in the best way the field of pharmaceutics, whereas they corrected me when my writing at the blackboard contained errors.

A special experience was the Leiden student association "Aesculapius", considering my German background where such activities of students' unions are still contaminated with a "haut gout". Many of the Aesculapius activities, such as symposia and excursions to neighboring countries, are parts of our education system. In the last 23 years I was helpful in the organization of such excursions and I participated with great pleasure in at least 7 trips to other European countries. And several times when I attended the Aesculapius meeting in which the old executive committee has to be formally discharged and the new one inaugurated, I waited until around 2 or 3 o'clock in the morning to finally effectuate the transition from the old executive boards to the new ones. In 1996, I became honorary member of Aesculapius and I am very proud of this honor. One of my colleagues told me: you may get a lot of scientific recognition but the most precious one is to be recognized, by your students as a good teacher.
My most expensive car-wash was also a deal with Aesculapius. During the 1995 Aesculapius symposium, the organization had to use my brand new Mercedes car because somebody forgot to bring a bouquet of flowers with him and they urgently needed a car to pick up the flowers on time. This was the first time that my new car was not driven by myself. Additionally, Aesculapius had also some financial problems. I donated 500 Dutch guilders and as a compensation for this donation and borrowing my car the Aesculapius board promised to wash it. It was not a real success story for me: when the students finally washed my car in front of the Gorlaeus Laboratories, two of my colleagues who did not know about the deal, accused me of exploiting the students in a way which was already history at Dutch universities for many years.

In 1984, just 3 years after my appointment in Leiden, the Dutch Government decided to close 2 of the 4 subfaculties of pharmacy, namely Amsterdam and Leiden. My family and me already made plans for the worst-case scenario to return to Germany. Fortunately our pharmacy school in Leiden was allowed to re-organize to a research

center called firstly Center for Bio-Pharmaceutical Sciences. Douwe Breimer played the leading role in this. All departments got the unique chance to reorganize themselves in the best way to become one of the leading research divisions in the world. When the chemistry divisions of the Vrije Universiteit Amsterdam joined us and the Leiden/Amsterdam Center for Drug Research was formed, a Research School was established, unique in the world and very successful both in research and teaching undergraduate and graduate students. I was and I am still very proud to be part of this Center. Probably my most prominent non-scientific contribution to this Graduate School was to name it Leiden/Amsterdam Center for Drug Research (abbreviated LACDR) and not Leiden/Amsterdam Institute for Drug Research, because the abbreviation LAIDR, although spelled differently in German, would mean "unfortunately" and this was to be avoided.

Scientifically LACDR performed really very well. Just about 8 months ago the evaluation of all departments by an international peer panel resulted in marks between very good and excellent, marks other research units in the world dream about. Since its inception this was the third peer review of the LACDR and all of them contributed to the improvement of the Center's performance.

In contrast to e.g. Germany, the basic teaching load at LACDR is and was very low. When I told my German colleagues that I have to lecture 12 hours they always asked "in one week, what a heavy task?" and when I said "no" the following question was "in one month?" And again the answer was "no". They normally could not believe that it was the teaching load for one year. Some of my foreign colleagues may have got the impression that our education system was very poor and especially in the beginning I often heard the question with a pitiful undertone "How long you still have to stay in the Netherlands?" and my answer to this question was always that I love to stay here. Why? Because this Dutch university system is much more flexible and effective in education and research than in other countries.

Teaching undergraduates and graduates the latest research developments and not to be bound onto a catalogue of sometimes boring topics which have to be lectured, I really felt the freedom of teaching pharmaceutical sciences and enjoyed my small teaching load with the clear direction to make the best of it.

To not leave you with a wrong impression that 12 hours were the total teaching load in the division of pharmaceutics, the total number was much higher because I had to share it with my colleagues in the department, but it was still moderate in comparison to other countries. Without any doubt, also the evaluation of the teachers by the students in the presence of the study advisor improved the teaching quality and most of the critical remarks of the students were implemented and improved the quality of teaching.

I often thought about this teaching load and questioned myself whether my students are worse educated than other students. My answer to this question was always "no", because I believe that the Dutch teaching culture at universities is different from other countries. Here in The Netherlands the pupils are already trained at secondary school before joining the university to learn and study much more independently.

Although their real knowledge of facts may be less than that of other students, their better training of conceptual thinking to solve problems makes them much more flexible and suitable in a changing world where knowledge doubles in about every ten years or less.

A university is not an ivory tower in which you do research, you also have to communicate with the outside world. We knew when we moved from Germany to the Netherlands in 1981, that the Dutch sympathy for Germans was still very restricted. Furthermore, many Germans visiting the Netherlands did and still do not know a lot about the second world war and post second world war history of the Netherlands. This fact also may create a lot of problems and does not increase the sympathy for Germany. I still appreciate the unique attitude of our neighbors in Rijnsburg where we lived when the first time the 4th and 5th May were celebrated. The 4th May is to remember all those who have died during the Second World War and the 5th May is the feast to celebrate the liberation from the Germans. Our neighbors came to us in the evening of 4th May and explained to us their historical perspective of the situation and emphasized that this has nothing to do with us personally. This helped us a lot to understand the Dutch feelings.
Another key experience in the very beginning of my stay in Leiden for me was the conversation with an old man with two crutches, whom I picked up with my car at the highway just outside of Leiden when I drove back to Germany. He told me that he was forced to work for the Nazis when the Netherlands were occupied, but that he could run away, was then captured again and was brought to Dachau. At Christmas' eve in 1943 a drunken Nazi broke his arm and legs with an iron pole. He survived, but since that time he was handicapped and unable to have a normal life. He was from Soest and came to Leiden to get new crutches. When I brought him to his home in Soest he thanked me and told me that he had since many years no bad feelings against the Germans anymore. I prayed that this was really true.
As a fact I had never a clash with somebody because of my German nationality inside and outside the university, although sometimes people told me the difference between friends and neighbors: your friend you can choose, your neighbor not.
In 1989 when the German re-unification became a fact, the anti German feelings in the Netherlands again increased. Political Den Haag was against the re-unification and the fear of a strong Germany was also felt very strongly among the population of this country. When it culminated, I watched a Dutch TV program in which it was reported that a female teacher for 6 years old children was fearing that the Nazis would come back to gas all the children. Germany was lucky to have at this time the best ambassador here in The Hague, namely Otto von der Gablentz (whom I had the privilege to know personally very well) and who was also a good friend of the late Prince Claus of the Netherlands (a German as well) and it is certainly their merit that the waves have been smoothed and finally the German re-unification was also accepted in the Netherlands.

In 1995 on the occasion of the 50th anniversary of the end of World War II, Queen Beatrix gave her famous speech encouraging her fellow countrymen to reconcile with their neighbors in the East. Since that time the relationship between both countries improved, also strongly supported by writers as e.g. Tessa de Loo. In her book "The Twins" (de tweeling), two originally Dutch sisters have been separated just before the beginning of the second world war and been brought to relatives both in Germany and the Netherlands. After the war they lost contact and met many years later by accident in the place Spa in Belgium. With a lot of empathy the author tells the stories of both sisters and the initial non-understanding of the situation during and after the war both in the Netherlands and in Germany and at the end the mutual understanding by the twins of the German and the Dutch situation. The movie made in The Netherlands from this twin story was just chosen some weeks ago as the best Dutch movie of 2003 with the motivation that this movie also attracts the elderly Dutch population. This fact also gives hope for a better understanding between both nations.
I also sincerely hope that the next Clingendael Report, the Dutch Institute of foreign relationships, will come to a better result of how the Dutch junior citizens estimate their neighboring countries. In the report from 1997, Germany was still at the end of the scale of popularity, although the great majority of the kids interviewed never have been to Germany before. There is certainly still a latent unpopularity of Germany and this should be changed by more goodwill not only when the Dutch team plays football or soccer against the Mannschaft of Germany. H.W. von der Donk characterizes football games between these two countries as "continuation of the war with friendly tools", especially enforced by the fact that Germany won in 1974 the soccer world cup against Holland. I do hope that this Dutch trauma of Munich will become past history in the near future.
You may understand that there are many good reasons why I spent some time on this topic: one of my main goals here in the Netherlands was always to be also a good ambassador for Germany and if I have succeeded to be one, I will be very glad and satisfied. Fortunately, I am not a good football player!

Back to the LACDR. Besides performing good research and a good teaching program for undergraduates and Ph.D. students, the third mission of the Center is to also collaborate with the pharmaceutical industry. For a department of Pharmaceutics and Drug Delivery this was never a problem. When I recall the situation around 1980 in Germany at that time correctly, collaboration with industry was something unethical you should not do. Why? Because you must be aware that your freedom of research could be jeopardized due to the binding restrictions of the contracts with the industry. Leiden University and LACDR facilitated industrial collaboration from the very beginning in a really professional way. There was always a liaison officer with a responsibility of the contracts and at least in the beginning a committee which checked the scientific merits of the industrial project. As a result of this we never per-

formed routine research for pharmaceutical companies, we always worked for mutual scientific benefits. The resulting philosophy was to use the Ph.D. positions from the first money stream paid by the university for basic research and to check with the industrial projects the fundamentals in the industrial practice. We always have been good partners to the pharmaceutical industry. I will illustrate this with only one example. In 1982 we started collaboration with the Schwarz company and continued for 20 years without interruption until today where still two projects are going on. And many other research projects with industry partners around the world followed and have been successful as well.

My certainly most exotic collaboration started in June 1984 when two gentlemen from Aruba, one of the Dutch Antilles islands, visited me here in Leiden. Honestly speaking at that time I did not know what Aruba was and means. The gentlemen wanted me to help them to develop cosmetic products based on aloe vera which is wild growing on the island. After a long beating about the bush I finally agreed to come to Aruba, a decision which lightened the burden of the two gentlemen very much and which was the start to a still existing and very fruitful and successful collaboration. At the end of my academic career I can say that I have developed more than 80 cosmetic products which are really on the market for sale and which are sold with great success on the Caribbean island and within the United States. The market chances in the Netherlands still have to be explored. The products are continuously updated under very severe quality control conditions comparable to those of the pharmaceutical industry for which I am responsible. As a consequence I went at least since 1984 once per year to Aruba, a fact which certainly was the basis for my today's nickname "Flying Dutchman"!

To summarize this chapter in Leiden, I think we are one of the most successful divisions if not the most successful one of LACDR with regard to collaboration with the pharmaceutical industry.

Another situation which gave me enormous freedom to get also involved in other duties was the fact that all departments have two regular assistant or associate professor positions. If you fill them in with excellent researchers (and I was happy to always succeed in this) you also have some time available to serve scientific organizations without neglecting your Ph.D. students and your industrial projects.

In the autumn of 1985 I was asked to become the president of APV (Association for Pharmaceutical Technology) and to additionally organize the next APV Congress in Leiden. The date was planned in the middle of April 1986 when the tulips normally are in full bloom. However, the winter before was so cold that at the congress only the leaves of the tulips were out of the ground but no flowers. In my introductory remarks to the congress I showed some pictures of how it should look like when square miles of the ground in the neighborhood of Leiden are in red, yellow and pink colors. Only later I recognized the influence of flowers on the memory of participants at a congress. Many years later a lady told me that she still remembered the Leiden APV congress quite well, not the scientific lectures and posters but my tulip slides. This is

another reason why this lecture today is not a predominantly scientific one, because in this case you would forget it very quickly as well!

During this congress I was elected APV president without having been before on the Executive Board of the society. The next years were quite tough and I was faced with almost bankruptcy of APV due to the investment in a wrong computer fed with more or less useless information. My Board helped me a lot in this time and after 4 years when I left APV as president the society was again financially sound. The only thing I regret is that my Board did not go with me to organize the 1990 APV congress in Dresden in the former German Democratic Republic. After the re-unification of Germany it would have been the first congress organized there.

In 1994 I was elected president of the Controlled Release Society, an American based international society. During that time I learned a lot about managing the club. Although the American system is quite efficient in getting a new officer worked in during the term as vice president and president-elect, the only one year period as president is too short to be really effective within such a structured organization and most decisions are taken by the general manager.

The last example. In September 1993 I was invited by my dear colleague Daan Crommelin to give a lecture during the FIP Congress in Tokyo in Japan. With pleasure, I accepted this invitation to have a chance to visit this fascinating country. However, I did not anticipate the real purpose of this invitation. Daan at that time was Scientific Secretary of FIP, the International Pharmaceutical Federation. During the Gala dinner I was approached by my good friend Kamal Midha, Chairman of the Board of Pharmaceutical Sciences, whether I would be interested in becoming the successor of Daan as Scientific Secretary of FIP in 1995. This was also the reason for this invitation! I accepted to become the 4th Scientific Secretary in a famous row starting with my predecessor Ko Polderman, continued by Douwe Breimer and Daan Crommelin. Just two months ago I finished my second term having then served 8 years for FIP, primarily representing the scientists around the world within FIP. With also having the new and 5th Scientific Secretary attending this lecture, namely Dr. Vinod Shah from FDA, we certainly have nearly 40 years of FIP history today in this venerable building of Leiden University!

Because representatives from all societies for which I served are here today, I cannot have done a too bad job. But most of you know that I can be very to the point, tough and thus not always easy to handle, but at the end of my scientific career I have learned a lot of diplomacy and we have solved most of our problems in an amicable way. Serving all these societies over the years my maxim always was that the society has the highest priority before my own benefit.

"To love what you do and feel that it matters – how could anything be more fun?" To my opinion this citation of Katherine Graham describes very well the work of a university professor. I liked my work very much. I never could understand when people said that they are happy to close the door of their working place behind them and go for 3 weeks of holidays. I never had these feelings. I really loved my work. To spend many hours during the weekends at the department was never wasted time.
Walt Disney once said: it is a special kind of fun to do the impossible, and I agree with this. To do the impossible started when Harry Boddé and Joke Bouwstra matured so far in their skin and transdermal delivery systems research that they needed no further help from me. Although not a very smoothly going process, I finally decided to look for another research topic. The newly chosen topic was to try to make the mucosal delivery of peptides and proteins and their absorption feasible. You have heard in the last two days some of our achievements presented by my own co-workers and in all modesty I think we have made some progress especially on the approaches of mucosal immunization, where my remaining Ph.D. students have successfully worked on and are still working on. In retrospective also the second change of a research topic was a good decision following the motto: if you can dream it, you can do it!

After the successful decoding of the human genome pharmaceutical sciences have entered a new era with a lot of expected break-through in the future. As the computer has revolutionized our daily life in the last years in a really unexpected way, the post genomic era will do the same in an even more radical way both in terms of diagnostics and therapeutics. Basically it must be easy: you only need zero and one in your computer and the 4 DNA bases and life can be decoded by what we today call "bioinformatics". Whether it is really so easy or only one of the many hypes we already have passed, remains to be determined. I have never heard in the last years about so many paradigm shifts in research and completely new insights that I do hope that our descendants in 50 years are of the same opinion about the real impact of our current scientific work. Whatever will be the truth, it is hoped that it will be only for the benefit of mankind.
At the end of your scientific career at Leiden University you will question yourself: What did you and we achieve in the last 20 years in drug delivery? Which progress did we make? I think the honest answer is disappointing: we still do not have delivery systems on the market which are able to deliver the drug "on demand" for optimal drug therapy avoiding toxic side effects. We still do not have so-called "closed-loop systems" or "feed-back systems" to achieve this goal. But we certainly have been able to show the way how to go further on, what are the merits of safe polymeric penetration enhancers, what type of delivery systems have to be designed to make oral peptide absorption feasible. And even more advanced: the transdermal intophoretic approach with potent drugs to treat the Parkinson disease could also be used to measure even not kinetic effects, but also to measure disease parameters as stiffness of

the Parkinson patient or the shaking frequency of his hands. This really will allow optimal drug therapy "on-demand". The chip technology has matured so far in the meantime that the external measurements of such disease parameters became already feasible.

But will such sophisticated delivery systems be further developed by the pharmaceutical industry? I doubt. In a time of economic depression and strong and unpopular cuts in the health care systems in most countries such systems will not be affordable in the years to come. If we believe the gurus in the next 10 years, more than 80 % of all drugs will still be administered as conventional dosage forms for oral delivery and only a few percent will belong to the class of novel sophisticated systems.

To my opinion the post genomic era will focus more on the direction of individualized drug therapy. After having decoded all our personal genome patterns, we will among other information know whether we are normal, poor or hyper metabolizers of a certain drug with as a positive result an optimized drug therapy. I do not believe that completely individualized drug therapy will become reality soon - if at all - due to the immense costs which would be involved to achieve real personalized drug therapy. Also the health care providers and health care politics in more general terms will not like to see us getting too old. In the future there will be an increasing gap between what will be feasible in both optimized drug therapy and drug delivery and on the other side what can we afford to pay.

Many of you here may already have had the same feelings that just after having finished his or her Ph.D. thesis the topic became really interesting. The same holds if you decide to retire and you will finish your scientific career: now the research especially in the field of vaccine research and delivery is really becoming exciting. I do hope that we will have soon more genetically engineered potent vaccines suitable for mucosal delivery. Nevertheless, we have to stop at one point. I decided to go with early retirement after having had so far an exceptional life. However, all my successes never would have become reality without my staff members, Ph.D. students, technicians and postdocs. I especially would like to thank Joke Bouwstra, Coos Verhoef and Gerrit Borchard for their support and collaboration over many years.

At this moment I personally feel like being a medicine, the shelf-life of which has now expired, but in which 97% of the active ingredient are still intact. I do not call myself to rest from this hobby called science, but would like to continue with the remaining intact brain in other interesting fields at other universities, and I do sincerely hope that you all will stay in contact with me and remain in my near in the years to come.

Ik heb gezegd.