An Interview with a Distinguished Pharmaceutical Scientist

Douwe D. Breimer–Elected Foreign Associate Member of the Institute of Medicine of the National Academy of Sciences of the U.S.A. (1999)[2]

Douwe D. Breimer, Ph.D. (1943) is Professor of Pharmacology at Leiden University, The Netherlands and Director of Research of the Leiden/Amsterdam Center for Drug Research. He received his pharmacy training from the University of Groningen and his Ph.D. on a thesis concerning "the pharmacokinetics of hypnotic drugs" from the University of Nijmegen with Professor J.M. van Rossum. In 1975 he was appointed full professor of pharmacology at Leiden University, Faculty of Pharmacy, which was transformed into a (Research) Center for Bio-Pharmaceutical Sciences in 1984. He became the Center's first Chairman and subsequently Director of Research when it merged with the Department of Pharmacochemistry of the Vrije Universiteit Amsterdam to become the "Leiden/Amsterdam Center for Drug Research". He also founded and became chairman of the Centre for Human Drug Research in Leiden and First Chairman of ULLA, which is an European Consortium for collaboration in pharmaceutical research training between the Universities of Uppsala, Leiden, London and Amsterdam, later on joined by Copenhagen and Paris-Sud.

Professor Breimer's research interests are in the areas of pharmacokinetics and pharmacodynamics, drug metabolism, biopharmaceutics and clinical pharmacology. He is (co)-author of more than 550 scientific publications and has received numerous awards and honours for his research accomplishments including: honorary doctorates from the Semmelweis University in Budapest (1989), the University of Gent (1990), the University of Uppsala (1992) and the University of Navarra in Pamplona (1998), the Nagai Foundation Award in Tokyo (1987), the Flückiger Medal from the German and Swiss Pharmaceutical Societies (1987), the Høst Madsen Medal (1993) from the International Pharmaceutical Federation, the Dirk van Os penning from the University of Groningen (1998). He is a Fellow of the American Association of Pharmaceutical Scientists (AAPS) (1990), Honorary Fellow of the American College of Clinical Pharmacology (ACCP) (1995), Correspondant Etranger de l'Académie Nationale de Pharmacie in Paris (1993), Foreign Member of the Royal Medical Academy of Belgium (1996). He was the Riegelman Lecturer at UCSF (1986), King's College Lecturer in London (1995), the Barré Lecturer in Montreal (1997).[1] In 1986 Professor Breimer was appointed life time member of the Royal Netherlands Academy of Arts and Sciences (KNAW) in Amsterdam and he is currently Chairman of its Section of Medicine. In 1996 he was appointed Vice-President of the Governing Board of the Dutch Scientific Research Organisation (NWO) which is the major research-funding organisation in The Netherlands. He was Scientific Secretary of the International Pharmaceutical Federation (FIP) from 1978-1989 and he is currently Past-President of the European Federation for Pharmaceutical Sciences (EUFEPS) of which he is also a co-founder.

Professor Breimer was Editor for Europe of Pharmaceutical Research (1989–1994) and is on the editorial board of several scientific journals including: *Clinical Pharmacokinetics, Clinical Pharmacology & Therapeutics, Journal of Pharmacokinetics and Biopharmaceutics, Pharmacogenetics, Journal of Pharmacy and Pharmacology, Xenobiotica, Journal of Controlled Release, Journal of Drug Targeting, Therapeutic Drug Monitoring, Pharmaceutical Science & Technology Today.*

WHAT DO YOU THINK HOLDS THE KEY TO YOUR SUCCESS AS A PHARMACEUTICAL SCIENTIST?

Response: In retrospect I think that a number of factors have contributed to that. First, my indecisiveness to study either

[1] Louis W. Busse Lecturer at the University of Wisconsin, Madison, Wisconsin (1997).

[2] To whom correspondence should be addressed at Universiteit Leiden, Gorlaeus Laboratories, P.O. Box 9502, 2300 RA Leiden, The Netherlands. (e-mail: breimer@lacdr.leidenuniv.nl)

0724-8741/00/0100-0001$18.00/0

chemistry, or biology, or physics. I was relatively good at and interested in each of those subjects in high school, but could not make up my mind which to choose for academic studies. Then an advisor suggested pharmacy, which is of course an excellent combination of those subjects. But I had not thought of that myself, because I grew up on a farm in small village, where the medical doctor did the dispensing.

So I started pharmacy out of interest in the subject matter rather than the profession, which I had never been in touch with. Subsequently I experienced a stimulating and research oriented atmosphere at the Faculty of Pharmacy, University of Groningen. During my undergraduate studies my mentor, Professor Jan Faber, took me already to an international scientific congress in medicinal chemistry in Germany and he organized a 3 months' research training period for me with Professor John Stenlake at the University of Strathclyde, Glasgow. That's where I obtained my first hands on research experience by separating the enantiomers of guanoxan, while the pharmacologists (Professor Bill Bowman) studied the stereoselectivity of the drug's action. On the basis of this work I read my first scientific paper at the British Pharmaceutical Society meeting in Birmingham in 1967. This was a nerve-wracking experience, remember, I was still only an undergraduate student.

But I was caught by doing pharmaceutical research and through reading the literature I also became fascinated by emerging topics in the pharmaceutical sciences, which at that time (late sixties) were biopharmaceutics (Professor G. Levy), pharmacokinetics (Professor S. Riegelman) and drug metabolism (Professor Arnold Beckett). In The Netherlands the place to go for such new subjects was the Department of Pharmacology at the University of Nijmegen, with Professor Van Rossum and Professor Ariëns, and I was fortunate enough to get a Ph.D.-position offered to work on the pharmacokinetics of hypnotics, both in experimental animals and in humans. Those were exciting 4 years, I learnt a great deal, did lots of experiments and met numerous international top scientists who passed through the department regularly. After that there was a call to be appointed at the newly created chair in pharmacology at the Faculty of Pharmacy, Leiden University. Although in my own view too early in my career (I should have liked to spend some time abroad), I took the opportunity when it presented itself and started from scratch in building up a new department in Leiden. And those subsequent 25 years have again been very stimulating and fascinating, in particular because of the many outstanding undergraduate, graduate and postdoctoral students who have contributed so much in putting the research of my group on the map to become internationally recognized. May be the key to success in my case has been a combination of meeting the right people at the right time and seizing the right opportunities at the right time.

WHAT ARE THE ACHIEVEMENTS THAT YOU ARE MOST PROUD OF AND WHY?

Response: First, the successful way that my chair in pharmacology at Leiden University has developed and has become recognized through its relevant research accomplishments. These relate to pharmacokinetics, pharmacodynamics, biopharmaceutics, drug metabolism, drug delivery, etc. In my Høst Madsen Medal Lecture in Tokyo (1993) I have explained how these subjects were inter-related by giving it the title "From the rectum to the brain, from probe to cocktail and from kinetics to dynamics." I owe our recognition very much to the numerous Ph.D.-students that passed through my department (shortly I will act for the 50th time as promotor of a Ph.D.-thesis) and I am proud to see how their careers have subsequently developed. I am also very much indebted to and proud of my two permanent staff members over the years, Dr. Meindert Danhof who is now directing a very successful PK/PD research programme and Dr. Bert de Boer who is heading our research on drug transport across the blood brain barrier.

From an institutional perspective I am pleased that the transformation of the Faculty of Pharmacy into a (Research) Center for Bio-Pharmaceutical Sciences became very successful and I am proud that I was able to coordinate this unique operation and that excellent scientists could be appointed on new chairs and staff positions. The subsequent merger of this Center in 1991 with the Department of Pharmacochemistry of the Vrije Universiteit Amsterdam to become the current inter-university research school "Leiden/Amsterdam Center for Drug Research" was a logical next step and I am proud of being Director of Research of this Center ever since together with my colleague and friend Professor Henk Timmerman in Amsterdam. Another milestone has been the establishment of the Centre for Human Drug Research in Leiden, which is an independent foundation and facility for performing innovative clinical pharmacological research.

I also think that I have overall been able to contribute to increased recognition and appreciation of the pharmaceutical sciences among the other sciences at the national and the international level. Example: before I came to Leiden the subject of pharmacology in the pharmacy curriculum was taught by the professor of pharmacology from the Faculty of Medicine; nowadays this situation has been reversed: our Center is now providing the teaching and research in pharmacology to the Faculty of Medicine. Furthermore in 1987 I was appointed life member of the Royal Netherlands Academy of Arts and Sciences, as the first pharmaceutical scientist since decades and was elected to become Chairman of the Academy's Section of Medicine in 1995. And although the pharmaceutical sciences have never been well recognized among the research funding organizations, I was appointed Vice-President of the National Dutch Research Organization in 1996 for 5 years.

CAN YOU NAME INDIVIDUALS WHO HAVE MADE A DIFFERENCE IN YOUR CAREER?

Response: I already mentioned Professor Jan Faber in Groningen, who apparently identified talents in me for pursuing a research career while I was still an undergraduate student. He was my mentor, encouraged me and opened doors nationally and internationally. In Nijmegen Professor Jacques van Rossum became my supervisor; he is a brilliant pharmacologist, both in dynamics and kinetics. Already in the early seventies he emphasized the relevance of the clearance concept and its physiological significance in drug disposition and until today I feel that he has not been sufficiently recognized for his pivotal contributions and insights in the fundamentals of pharmacokinetics. I remember very well how surprised I was at an international congress in 1975, hearing colleagues from the U.S. talking about an important new concept in pharmacokinetics (clearance), while I had been brought up with that concept from the

day onwards that I entered the Department of Pharmacology in Nijmegen in 1970!

My career has much been inspired by colleagues with similar interests and whom I still look up to, like Professors Gary Levy, the late Sid Riegelman (I had planned a sabbatical with him), Arnold Beckett, Peter Speiser, Les Benet, Lew Sheiner, Ron Borchardt, Malcolm Rowland, Lennart Paalzow, Joe Robinson, Geoff Tucker, Ernst Mutschler. In 1976 I met with Dr. John Urquhart, at that time still at ALZA, and he has been a continuous source of inspiration ever since. The same holds for Dr. Carl Peck, who did a sabbatical with us in Leiden the year after he left the FDA. In Japan Professor T. Nagai has been instrumental to introduce me to numerous important scientific contacts in Japan, like Professors Sugiyama and Hashida. It is in fact extremely rewarding to have so many personal contacts with fellow scientists all over the world, several of which have developed into personal friendships.

WHAT ARE THE FUTURE CHALLENGES TO THE PHARMACEUTICAL SCIENCES?

Response: Pharmaceutical sciences stands in my view broadly for the advancement of innovative drug research and development. It comprises the discovery of biologically active compounds, their optimization of properties by understanding their mechanism of action and disposition, their formulation, delivery and targeting to their site of action, their efficacy and safety assessment and their utilization. And the challenges and opportunities are greater than ever. Further understanding of the human genome and its functionality at the protein and cellular level will result in hundreds, or even thousands, of new drug targets related to specific pathophysiological mechanisms. This will "fractionate" human disease in numerous subclasses, which will potentially enhance the specificity of drug treatment, i.e. therapies will become more inidividualized and tailor-made. Target identification will give rise to lead identification through combinatorial chemistry and high-throughput screening technologies with numerous lead options. However, new lead is not yet a new medicine with proven efficacy, safety and quality.

And here lies in my view an important challenge to the pharmaceutical sciences *per se*, i.e. to enhance the predictive power of the information collected during early non-clinical phases of drug development with high precision. For the pharmaceutical industry this means a forward integration of drug development and drug discovery, i.e. shifting the attrition of non-promising molecules from the resource-intensive human phases to substanially earlier phases in the development process. And here I quote Dr. Theo Guenthert (Roche, Basel) from a recent Workshop that ECPM and LACDR organized jointly on "Streamlining Proof of Principle" saying that this process requires "parallel multi-dimensional optimization: improving several key properties of a lead compound simultaneously rather than sequentially". This concept recognizes that maximization of the desired features in one dimension (e.g. receptor affinity *in vitro*) may render other properties that are incompatible with the overall *in vivo* target profile (e.g. orally available, reaching the target site in the CNS, devoid of high inter-subject variability in drug metabolism). Academic groups are in my view challenged to contribute to this new paradigm in drug research and development by fostering new fundamental concepts and new technologies in drug transport, delivery and targeting, in formulation research, in physiologically-based drug disposition and metabolism, in pharmacokinetics integrated with pharmacodynamics, in safety assessment by an improved understanding of the molecular mechanisms of toxicity and by exploration of the field of toxicogenomics.

Also a major challenge is linking and validating genetic, biochemical, pharmacological and other markers for diagnostic, efficacy and safety evaluation, thereby enhancing proof of concept for further clinical development. New informatics, analytical, visualization, modelling and simulation techniques are required to be able to operate at a far higher resolution and prediction level than is currently the case. I do not believe that the "in silico drug development" will take place as quickly as recently suggested in two reports on the pharmaceutical industry by Pricewaterhouse Coopers, but there definitely will be important developments into that direction. These are exciting times to be a pharmaceutical scientist!

WHAT IS YOUR VIEW ON PK/PD RESEARCH, NOW AND IN THE FUTURE?

Response: I consider it the primary objective of PK/PD research to identify key properties of a drug *in vivo*, which allow the characterization and prediction (through appropriate modelling) of the time course of drug effects (intensity and duration) under normal and pathophysiological conditions. It constitutes *the* scientific basis for optimal drug dosage regimen. Since 1990 our Center in Leiden has organized 3 international symposia in this field, entitled "Measurement and kinetics of *in vivo* drug effects" with all the leading scientists presenting their latest views and results. In 1990 much emphasis was placed on mathematical and empirical PK/PD modelling concepts and on the measurement of relevant *in vivo* pharmacological effects. The latter is still a major challenge and most important in the context of the discussion on acceptance of "surrogate" effects versus clinical endpoints. In 1994 the emphasis had shifted towards physiological modelling and factors influencing PK/PD relationships, like tolerance development, drug interactions, delivery patterns etc. Also much attention was paid to PK/PD strategies in drug development and to population approaches. In 1998 mechanism-based PK/PD modelling was highlighted, which takes into account the various mechanisms in drug disposition and drug effects at the receptor level.

Characterization of transport to the site of action (including the role of various influx and efflux transporters) is an important issue, as well as *in vivo* drug receptor (or enzyme) interactions. *In vivo* many factors may attenuate and modulate interactions, including variability in receptor activity and the existence of genetic polymorphism in receptor (or enzyme) expression. It will be a major challenge to identify and disseminate such factors and to translate such information into optimal dosage requirements in individual patients. Modelling and simulation techniques will further develop for advanced PK/PD data analysis for continuous as well as non-continuous drug effects, taking all types of non-linearities into account, which will bring the field closer to clinical relevance. One of my favourite topics to lecture on is the relevance of PK/PD for drug delivery research. PK/PD research will in principle provide the information needed to define optimal rate and time programming of delivery of a specific drug. There is much to be gained if there

was more integration between these fields of pharmaceutical research.

AS PHARMACEUTICAL RESEARCH IS TAKING ON AN INCREASINGLY MOLECULAR AND CELLULAR THRUST, ARE YOU CONCERNED THAT OVER TIME, THERE WILL BE NO ONE TRAINED IN THE TENETS OF CLASSICAL PHARMACOKINETICS AND PHARMACODYNAMICS?

Response: Yes, there is indeed major emphasis in the biomedical and bio-pharmaceutical sciences on the fundamental understanding of genetic, molecular and cellular regulation of (patho)-physiological function. And for good reasons, because that's where we must start for new target finding and rational lead finding of new drugs, as well as for innovative drug delivery and targeting strategies. Nevertheless, the complexities of a living system is still far beyond our current understanding and definitely not just the summing up or integration of the in itself impressive amount of information obtained in *in vitro* systems. Predictive power from *in vitro* to *in vivo* has recently increased in certain areas (drug metabolism, drug absorption), but not for total body pharmacokinetics and certainly not for physiological, pharmacological or toxicological effects. "The proof of the pudding is in the eating" is and will remain a major issue in drug research and development and in order to do that properly, well trained and qualified scientists are needed.

This leads me back to the question whether or not I am concerned with the molecular trend in research and diminished interest in *in vivo* experimentation necessary for (classical) pharmacokinetics and pharmacodynamics. That is indeed a concern to me, not just because of the trend in research, but in particular because of the severe restrictions induced by anti-vivisectionist movements associated with *in vivo* experimentation. In some countries one is almost considered a criminal if being involved in such research. That is not particularly motivating to young students to be associated with. In addition research funding organizations have over the past 15 years heavily invested in the genetic and molecular sciences, with low priority to "classical" *in vivo* physiology or pharmacology. In several countries pharmacological societies have expressed severe concern on this development, because it has indeed lead to lack of well trained people. On the other hand, I see a reverse trend caused by pressure from the genetic and molecular side for *in vivo* expertise to define function of for example specific proteins. This is clear from the enormous boost in genetic knock-out technologies. We have recently invested heavily in making intracerebral microdialysis operational in knock-out mice lacking different transporter proteins at the level of the blood-brain and CSF barrier. It is this type of "molecular *in vivo* pharmacology" that will help to revive overall interest in pharmacokinetics and pharmacodynamics.

SCIENCE IS BECOMING INCREASINGLY MULTIDISCIPLINARY. HOW CAN ONE ESTABLISH AND MAINTAIN HIS/HER RESEARCH IDENTITY IN THAT ENVIRONMENT?

Response: In my view research identitity and recognition is in the first place achieved by scientific excellence. And of course that is associated with a focussed theme of research, which in the pharmaceutical sciences in order to excel is often of an inter-disciplinary nature. Here multidisciplinarity is not an objective in itself, but intrinsic and rather a necessity in the search for new biologically active molecules, their action and disposition, delivery and targeting, etc. By "borrowing" and translating fundamental concepts from other disciplines into pharmaceutical research, new borders may be crossed, leading to new cutting edge principles and potential applications. Pharmaceutical scientists are uniquely trained to do this, not to become "a jack of all trades and a master of none", but to achieve scientific depth and excellence in there own right. In our Leiden/Amsterdam Center for Drug Research, our 9 Divisions represent the "classical" pharmaceutical disciplines as "expertise bases." However, the programme of our Center's research is organized in fewer "major research themes" to each of which more than one discipline is contributing (like in a matrix structure). In our annual Progress Report we report on research progress in these themes, not in the disciplines.

SCIENCE IS ALSO BECOMING INCREASINGLY GLOBAL. IN ANY MAJOR SCIENTIFIC MEETING THERE IS A HEALTHY MIX OF SCIENTISTS FROM ALL OVER THE WORLD. WHAT PURPOSE THEN WOULD REGIONAL (ASIAN, EUROPEAN, NORTH AMERICAN, ETC.) SCIENTIFIC MEETINGS SERVE?

Response: Scientific congresses and symposia offer platforms for scientists to meet. They fulfill in my view a very important role in the dissemination and exchange of the latest information and to contribute to the scientific debate, from person to person and in organized settings. And face to face interactions with colleagues and peers are far more inspiring than electronic or written interactions. They also fulfill in my view a certain benchmarking role: how does my research in terms of originality, methodologies, results, implications, compare to my competitors in the field? Yes, no doubt, our sciences have already become global. Any scientist that wishes to make an impact (and who doesn't), publishes in the English language in order to be read and hopefully recognized by colleagues anywhere in the world. Therefore in principle it would be desirable to organize global rather than regional meetings. However, it will take a while before that will be feasible from a financial and logistic point of view. In the mean time the reasons to meet, as I discussed them a few moments ago, remain equally valid and regional meetings are next best.

Until relatively short time ago the pharmaceutical sciences in Europe suffered from overall provincialism and lack of regional organization. This is one of the reasons why the initiative was taken to establish the European Federation for Pharmaceutical Sciences (EUFEPS) in 1990, which can be considered as the European counterpart of AAPS. It organizes a European Congress of Pharmaceutical Sciences every second year and more specialized meetings annually.

It is important to note that for the first time in 2000 a truly independent global congress in our field will be organized: the Millennial World Congress of Pharmaceutical Sciences in San Francisco, 16-20 April, with 21 plenary lectures and 42 symposia. I have had the pleasure to prepare for the programme of this meeting, together with Ron Borchardt, Yuichi Sugiyama,

Les Benet and regional committees, and I hope and trust that it will be a great success. For me it will also be a test case for the pharmaceutical sciences to explore how global its scientists really are: is there eagerness to meet colleagues from all over the world or are we still suffering from provincialism? This question holds equally for Europe, Asia as well as the Americas. I usually attend the AAPS Annual Congress and I am sometimes appalled by the lack of awareness among American colleagues, many of whom have never been out of the U.S., of what happens scientifically elsewhere in the world. The meeting in San Francisco offers a unique opportunity to change this and, if successful, I am sure that such a meeting will be repeated at least every 4 years moving from one corner of the globe to the other under the umbrella of the International Pharmaceutical Federation (FIP). For decades already pharmacologists, biochemists, and whatever self-respecting science have you, organize their global meeting every 4 years; why has it taken pharmaceutical scientists so long to follow?

YOU WERE EUROPEAN EDITOR FOR *PHARMACEUTICAL RESEARCH* IN ITS FORMATIVE YEARS. WHAT DO YOU THINK IS THE REALISTIC NICHE FOR THE JOURNAL IN THE COMMUNITY OF ELITE SCIENTIFIC JOURNALS? SHOULD THE JOURNAL STRIVE TO BE BROAD-BASED OR SHOULD IT SHARPEN ITS FOCUS IN A FEW FOUNDATION-BUILDING AREAS?

Response: I strongly believe in a broad-based journal that attracts publications representing all cutting edge science in our field of interest. It should in principle cover all new and relevant issues in drug research and development, with high quality as the decisive criterion for acceptance. *PharmRes* is in my view currently the flagship journal in the pharmaceutical sciences and in every issue I identify articles that truly contribute to the advancement of our field. As I discussed before in this interview, the intrinsic inter- or multidisciplinary nature of our field is relatively unique, that also calls for broad-based journals. At the time of the establishment of EUFEPS we also founded the *European Journal of Pharmaceutical Sciences (EJPS)*, not just to create another new journal, but to integrate a number of existing national or regional scientific pharmaceutical journals into one. Under the current editorship of Per Artursson in Uppsala this journal develops into a sound competitor of *PharmRes*. Both journals reflect a global scope in terms of attracting articles from all over the world; science is becoming global, didn't we say that before?

HAS YOUR PHILOSOPHY OF EDUCATING GRADUATE STUDENTS CHANGED OVER THE YEARS AND WHAT IS YOUR ADVICE TO JUNIOR SCIENTISTS PURSUING A CAREER IN THE PHARMACEUTICAL SCIENCES?

Response: The guidance of graduate students is still one of the most gratifying responsibilities for a senior academic scientist. In The Netherlands we are in the relatively fortunate position that undergraduate students in the sciences during their 4-5 years' curriculum are hands-on engaged in a research project (usually that of a Ph.D-student) for 6 to 12 months. This implies that they assume experimental skills, learn to read the scientific literature, design experiments, analyze and evaluate data and write a report comparable to an MSc-thesis in other countries. If they are subsequently selected for a Ph.D-position, they start with their experimental work almost from day 1 onwards until the completion of their Ph.D-thesis after 4 years. The thesis is printed in a minimum of 250 copies and usually consists of at least 5 chapters each representing a scientific paper already published or to be published in the international scientific literature. By that time the students have become rather independent scientists, who potentially could pursue a career on their own.

What has changed over the years is that initially (25 years ago in my case) hardly any course work was required, whereas now during their first two years Ph.D-students are supposed to follow several courses in parallel to their research. These range from enabling (e.g scientific writing) to specialized scientific or methodological ones. The reason is that the undergraduate curriculum has been shortened and has often become more specialized. Consequently, the outlook of the students has become narrower than it used to be, whereas according to my philosophy students need to assume scientific depth as well as breadth. Hence several years ago LACDR has started to organize courses for Ph.D-students, several of which can also be attended by external participants (is also a source of income for the Center!). Since not all required expertise is available in our Center and also in the context of the philosophy that students should be exposed to an international environment, we have taken the initiative in 1992 to establish ULLA (stands for Uppsala, London, Leiden, Amsterdam and recently joined by Copenhagen and Paris-Sud), which is a European Consortium for the advancement of graduate research training in the pharmaceutical sciences. Apart from regular exchange of staff and students among the members of the Consortium, the most important activity is the organization of a Summer School every second year for about 10 days at a specific (attractive) location. In 1999 this took place in Copenhagen, with about 150 students and 70 members of staff participating, during which 40 one-or two-day courses were offered ranging from "drug registration requirements" to "functional genomics" and "the use of cell culture techniques". Students are strongly advised to choose courses outside the domain of their own ongoing research. This will enhance their flexibility in pursuing a further career which will often not be in the same area as their research specialization.

WHAT WOULD BE YOUR ADVICE TO OUR SENIOR PHARMACEUTICAL SCIENTISTS IN THEIR RELATIONSHIP TO THEIR JUNIOR COLLEAGUES?

Response: In my view a clear responsibility of a senior scientist is to provide space, scientifically and physically, to their upcoming junior colleagues. They should be facilitators and fulfil the role of a mentor and always try to avoid that they are an obstacle in the way of development of a young colleague. This may imply a heavier task with respect to administration, coordination, representation, etc., functions which are necessary within

each research environment and also require experience. Senior scientists should make efforts to remain sources of inspiration rather than domination and create a stimulating research and training environment. It should also be realized in our field of research that "the turnover of science may be higher than the turnover of scientists", which means that the true cutting edge innovations often have to come from the new generations of scientists, i.e. the junior colleagues. Therefore, it is essential that in each research institute, within academia as well as in industry, there is a continuous throughflow of young people (Ph.D-students, postdocs) and a mechanism in place to select the truly brilliant ones and offer them a tenure track perspective.

DO YOU FEEL THAT WE ALL HAVE AN OBLIGATION TO BE A VOLUNTEER IN SCIENTIFIC ORGANIZATIONS? IF SO, WHY?

Response: Yes, definitely! Such organizations have been established for our own benefit and can only flourish with committed and active membership and elected officers. They offer the platforms for independent exchange of information and debate, they contribute to identity, recognition and visibility of a specific scientific field, they facilitate networking among its membership and I could mention several other pertinent roles. I am personally member of at least eight national and international scientific societies and I have served on numerous boards and committees. This is very time consuming, meetings are often in weekends and are often at one's own expense, but to contribute to the objectives of such organizations is also very rewarding. In recent years, I have spent much time on the establishment of the European Federation for Pharmaceutical Sciences (EUFEPS), which I mentioned before in this interview, as a co-founder, vice-president, president and past-president. It consists of national member societies in the various European countries and individual members. Starting such an organization without sufficient financial resources is an enormous task, but thanks to the strong support of the Swedish Pharmaceutical Society, a professional secretariat could be established in Stockholm. Through the strong efforts of several volunteers EUFEPS is developing steadily, but more could be achieved at higher speed if indeed even more leading European pharmaceutical scientists would be willing to offer their competence, experience and time. Indeed, I view this as an obligation and I hope that this part of the interview may actually serve as a call on individual pharmaceutical scientists to join and actively contribute to EUFEPS.

WHAT IS THE PLACE FOR COLLABORATION WITH INDUSTRY AND ENTREPRENEURSHIP IN ACADEMIA?

Response: In 1996, I wrote an Editorial on "University-industry collaboration in the pharmaceutical sciences" in the magazine *Drug Discovery Today* (DDT **1**, 403) quoting Dr. J. Drews, former VP for R&D of Roche on principles for inovation management in the pharmaceutical industry. He suggested that only the formation of functional links between groups can produce the broad scope of scientific opportunities that is needed to obtain a sufficiently large number of intelligent options for the development of novel drugs. It is less important in these days to achieve a critical mass in a given research area than to obtain a critical quality: i.e. it is necessary to integrate research groups (industry-academia, industry-industry, etc.) effectively into consortia of international scientific cooperation. And this has very much occurred in recent years, through mergers and strategic alliances.

For industry-academic collaborations in fundamental and strategic pharmaceutical research to be fruitful and to meet expectations on both sides, in my view a number of issues are important. On both sides the *scientific* benefit should be clearly defined (academia is not a CRO!) in terms of perspectives and expectations. The scientific input should preferably originate from both sides and be interactive. Patent protection is an essential issue for discoveries with a potential application; a patent protects and thereby encourages industrial investment, and at the same time discloses the finding, which is in agreement with the academic objective to publish. Collaboration should be guaranteed for a reasonable period of time and not subject to a constant debate on "go" or "no go" decisions. At the university level, conflicts of interest and of commitment should be avoided by both individual scientists and institutions. Individual conflicts may involve reduced commitment to the primary objective of the institution caused by financial or other interest in third parties and deviations from the standards of scientific conduct. The institution may be faced with challenges to research autonomy, such as priority conflicts, questions of "who funded what" and thereby on property rights, and on the freedom of publication and teaching. It is important that the management of a university institute has a clear and open policy on such matters, including incentives on collaborative efforts and alliances and also on opportunities for establishing spin-off companies. Such academic entrepreneurship in Europe should be encouraged and facilitated to a far greater extent than is currently the case.