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Interview with a Distinguished Pharmaceutical Scientist

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Bernard Testa graduated as a pharmacist and obtained a Ph.D. with a thesis on drug-macromolecule interactions. Following a two-year post-doctoral period at Chelsea College, University of London, he returned to the University of Lausanne, Switzerland, as an assistant professor, to become Professor and Head of Medicinal Chemistry in 1978. He also held the positions of Chairman of the Department of Pharmacy and Dean of the Faculty of Sciences. Currently and until the end of the 1999–2000 academic year, he is also President of the University Senate. Bernard Testa has edited 25 books and written 3 others (a 4th is reaching completion), one of which won a Citation Classic award in 1990. He (co)-authored over 350 research and review articles in the fields of drug design and drug metabolism. A member of the Editorial Board of several leading journals (e.g. Biochem. Pharmacol., Chirality, Drug Metab. Rev., J. Med. Chem., J. Pharm. Pharmacol., Med. Res. Rev., Pharm. Res. and Xenobiotica), he was for over 4 years the Editor—Europe of Pharmaceutical Research. Honors include Honorary Doctorates from the University of Montpellier (France), and the University of Parma (Italy), Fellowship in the Royal Society of Chemistry and the American Association of Pharmaceutical Scientists, Foreign Honorary Membership in the Belgian Royal Academy of Medicine, and the Chair of Honor of the Université Catholique de Louvain (Belgium) for the academic year 1992–93. Bernard Testa is a member of numerous other scientific societies such as the American Chemical Society, the European Federation for Pharmaceutical Sciences, the European Society of Biochemical Pharmacology, the International Society for the Study of Xenobiotics (Charter member), the New Swiss Chemical Society and the QSAR and Modelling Society. His hobbies, interests and passions include jogging, science fiction, epistemology, teaching and scientific exploration.

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

Response: This question is both deep and broad, and it is also a central one. Allow me therefore to answer it at some length and on a rather personal level. First of all of course, success is a relative concept which depends how you evaluate it and with what you compare it. It also contains qualitative and quantitative components. Today, scientific success is mostly a quantitative affair—success is *measured*. This is not how I feel.

I can accept to be considered a successful scientist not because my CV lists this number of papers, that number of books and various honors, but because I am *content* with what I have achieved—hoping of course to enjoy many more creative years. So why this "success"? There is of course some ambition, but I would state that the main reasons are two impulses I feel strongly, a) the urge to discover and create, and b) the urge to be worth and repay the blessings of my life. Aspiration to discovery is a characteristic of most if not all scientists, but I am not sure how many realize the full significance of this priviledge. I believe that we will never cease discovering, first because Creation is infinite, and also because discovery is in itself an act of creation. Far from being only spectators and actors, scientists like artists and others are also playwrights in a Universe in the making, as so beautifully argued by the philosopher Louise Young (1).

And then there is gratitude for what I am and have received! I owe beyond words to my late parents, who started from nothing and had the upbringing of their children as their first objective in life. I owe immensely to Switzerland, my country, who saved my Ashkenazi mother from the Nazis, protected my Italian father, and offered me a life of peace, study, fulfilment and beauty. Then there are my wife and children .....

WHAT ARE THE 2–3 ACHIEVEMENTS THAT YOU ARE MOST PROUD OF? WHY?

Response: When it comes to professional and scientific achievements, I must indeed confess taking pride in some of my former students, in the few books I wrote, in some symposia I co-organized, and in our Pharmacy building whose construction I coordinated. Together with Professor Peter Jenner in London, we have clarified the concepts of regio- and stereoselectivity in drug metabolism, and feel that this has greatly helped workers

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in the field. Our studies on the QSAR of dopamine antagonists have also made an impact. However, I would say that the greatest fun in recent years has been in the fields of lipophilicity and molecular modeling, going beyond the empirical to gain a deeper knowledge (2).

WHAT WAS THE TURNING POINT IN YOUR DISTINGUISHED CAREER?

Response: Very clearly this was the two year period I spent as a post-doctoral fellow at the University of London. The decision to apply for a Swiss National Science Foundation grant rather than entering the pharmaceutical industry was an easy one despite the financial appeal. This decision, and the two London years that followed, were critical in my becoming a medicinal chemist and then entering an academic career.

CAN YOU NAME THE TWO OR THREE INDIVIDUALS WHO HAVE MADE A DIFFERENCE IN YOUR CAREER? HOW SO?

Response: A number of individuals have influenced my career and will always have my gratitude. However, two persons occupy a very special place in my memory, and I thank you for the opportunity to mention them. Both persons were teachers of mine, in fact my first and my last mentor in chemistry. Dr. Arthur Desbiolles was my high-school chemistry professor, a rigorous, demanding and enthusiastic teacher who led me into an unsuspected and enchanting world. Torn between medicine which I was planning to study, and the fascination of chemistry, I chose both by becoming a pharmacist, alas a commercially ungifted one.

The second individual who had a major influence on my career was Professor Arnold H. Beckett, Head of pharmaceutical chemistry at Chelsea College, and my post-doctoral mentor. A scientist of exceptional versatility and vision, he was a pioneer in drug metabolism, medicinal stereochemistry, receptor topography, structure-permeation relations, molecular toxicology and doping control. Always on the move yet able to supervise closely 20 or more post-docs and graduate students, he made a deep impression on most of us. He helped me ask the right questions, plan the most informative experiments and recognize the significance of unexpected results. But above all, he taught me scientific writing. Thank you again, Joe, I hope you read this!

PHARMACEUTICAL SCIENTISTS ARE FACED WITH THE DILEMMA OF HAVING TO PUBLISH IN BIOMEDICAL OR BASIC SCIENCE JOURNALS AND HAVING TO PRESENT IN THEIR SPECIALTY MEETINGS IN ADDITION TO THE PHARMACEUTICAL SCIENCES VENUES. DOES IT MEAN THAT CUTTING EDGE SCIENCE WILL NOT LIKELY BE FEATURED IN THE PHARMACEUTICAL SCIENCES FORUM?

Response: This question seems to oppose basic sciences and pharmaceutical sciences, as well as their journals and symposia. Are we as pharmaceutical scientists really facing such a dichotomic situation? Perhaps we are, to some extent. But we just need to compare the contents of basic and pharmaceutical journals to see that the contrast is only partial. Below the differences, there is some overlap, but mainly there is complementarity. It is our good fortune that both types of journals receive our papers. Certainly a pharmaceutical scientist will choose to publish a groundbreaking theory or method in a basic journal, but this will quickly be followed by a string of submissions to pharmaceutical journals in order to explore, validate and apply this theory or method. In brief, I would say that some "cutting edge" science is also bound to appear in the pharmaceutical sciences forum.

YOU WERE, FOR THE PAST FIVE YEARS UNTIL APRIL 1998, THE EUROPEAN EDITOR OF PHARMACEUTICAL RESEARCH. 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: As discussed above, pharmaceutical journals have a major and specific role to play. I feel that they must strive for excellence in their own niche, and should not venture into a hopeless competition with the most prestigious basic journals. This is also true for *Pharmaceutical Research*, the world-leading pharmaceutical journal. I perceive *Pharmaceutical Research* as a complement and a partner to the élite journals, not as a competitor fighting for a share of high-visibility papers in the basic sciences. This would be a radical and potentially damaging change in its mission. Almost four years ago, in an Editorial to this journal (3), I commented on the mission of *Pharmaceutical Research* to publish "studies that answer meaningful questions, and raise new ones as seeds for deeper ideas and better [medicines]". More than ever, I am convinced that *Pharmaceutical Research* is doing very well in this direction.

Sharpening the focus of *Pharmaceutical Research* is a scenario I disagree with, for at least two reasons. First, research fronts fluctuate wildly and not always predictably. Today's fashionable fronts will certainly not be tomorrow's. By focusing on a few "foundation-building" areas, any journal may find itself lagging once the house has arisen above the foundations. A second reason is the *educational mission* of generalist journals, especially when, like *Pharmaceutical Research*, they are the prime medium of a major scientific society such as the AAPS. Perhaps my educator's glasses bias my vision, but I do believe that many pharmaceutical scientists read or at least scan *Pharmaceutical Research* not only for the latest advances in their specialty, but also to remain broadly knowledgeable.

WHAT ARE FUTURE CHALLENGES IN PHARMACEUTICAL SCIENCES?

Response: This is an essential question in the etymological sense. In other words, what is the *essence* of pharmaceutical sciences, what are its boundaries, and how might they evolve? In a recent editorial (4), I commented on the fuzzy boundaries of pharmaceutical sciences, making the point that our unifying banner is the *pharmakon*. I also noted that "various centrifugal trends can be felt that advocate an evolution of the pharmaceutical sciences to become more computational, physical or biomedical, and less directly connected with bioactive agents." This is a challenge faced by pharmaceutical sciences—to evolve, and evolve at a steady pace, but always retain the drug/medicine in close sight. By working to discover and improve drugs and medicines, we contribute knowledge and understanding and thus serve science, but we also contribute to the general welfare

and thus play a social role (5). Our challenge is to continue serving these two fundamental aspirations of humankind.

WHAT IS YOUR VIEW ON THE CURRENT STATE OF RESEARCH IN STRUCTURE-ACTIVITY RELATIONSHIP? WHAT ARE SOME EXAMPLES OF EXCITING DEVELOPMENTS?

Response: Yes, let's return to more delimited scientific issues. Structure-activity relationships (SARs) are my main playground. Very schematically, there are four components to SARs, namely:

- A) biological systems, i.e. any biological entity from a functional protein to a population of organisms;
- B) bioactive compounds (for example hits, lead compounds, drug candidates, drugs, toxins, pest-control agents);
- C) the biological responses of A) when exposed to B); and
- D) mathematical models describing how C) varies with variations in B).

Over the years, advances in SARs have been mostly in components B) and D), bearing in mind that fields A) and C) are primarily the provinces of biologists, biochemists and pharmacologists. Advances in field B) are experimental and computational and involve a deeper and broader understanding of molecules examined as dynamic stereo-electronic entities, i.e. in four dimensions. This is where and why lipophilicity is such an informative and relevant molecular property (2).

In field D), neural networks, genetic algorithms and new statistical tools have radically changed QSARs. A brilliant and particularly rewarding success has been the merging of molecular modeling and statistics to create powerful softwares (e.g. CoMFA) correlating molecular fields with biological activities. However, I am convinced that we have not reached the end of the road, and by far. Fluctuations in properties as a result of the dynamics of molecules remain a real challenge. The dynamics of agent-target complexes are not considered. On a more general level, I feel that SARs have much to offer in terms of interpreting mechanisms of action and understanding biological systems. Up to now however, SARs have been used mainly in the discovery and optimization of lead compounds. This is indeed a major objective of SARs, but it is not the only one.

WHAT ARE FUTURE CHALLENGES IN DRUG DESIGN?

Response: Drug design has reached impressive heights when it comes to optimizing a lead structure for a given macromolecular target (receptor, enzyme, nucleic acid, etc). The same is not yet true in pharmacokinetic optimization and targeting. Paradoxically, an optimal pharmacokinetic behavior is more difficult to predict and achieve rationally than optimal affinity for a target. Perhaps the factors involved are more complex and diverse in one case than in the other. But whatever the reasons, understanding and solving them is, I feel, a major challenge in drug design and more generally in drug research.

WHAT IMPACT DO COMBINATORIAL CHEMISTRY AND HIGH-THROUGHPUT METHODS HAVE ON DRUG RESEARCH?

Response: Combinatorial chemistry began as a technology and has evolved into a full science whose multidisciplinarity never ceases to amaze me. Here, we have connected developments in synthetic chemistry, informatics, robotics and other disciplines, which together have generated a methodology that is much greater than the sum of its parts. In other words, we have witnessed the emergence of a new science, the word "emergence" having here the meaning given by systems theory. But combinatorial chemistry alone would not be so useful in drug research, were it not for high-throughput methods of biological screening. The first of these methods were functional tests (bioassays), and here also research continues at a fast pace to increase their capacity, sensitivity and specificity. Furthermore, new high-capacity methods are now being developed to measure physicochemical properties, forecast *in vivo* absorption, distribution and metabolism, and screen for toxicity. Together, combinatorial chemistry and high-throughput methods form the experimental component of an emergent "super science," with virtual screening and database mining as computational counterparts. And there is more, since this "super science" is now entering in synergy with target identification, where genomics is becoming all-important. Truly, we are seeing a revolution in drug research, and one could go as far as saying that the 21st century began in the 90s.

However, nobody should underestimate the very long road that separates the myriads of compounds active on predefined *in vitro* targets, from the few drugs that come out of the pipeline and reach the market. There is more to a clinical response than the mere action at a single target, as there is more to a pharmacokinetic behavior than cell permeation and a few enzymatic reactions. This is why the new technologies cannot replace traditional methods in drug research, they simply precede them. There will always an indispensable role in drug research for lead optimization by synthetic and SAR methods, and for *in vivo* assessment of pharmacological, pharmacokinetic and toxicological properties.

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

Response: Multidisciplinarity means synergy, and synergy means new territories, new potentialities, new opportunities, new discoveries. As the scientific *context* (I feel "context" has a deeper meaning than "environment") (6) becomes richer in information and knowledge, it also becomes more fertile and allows new achievements. Should scientists maintain their research identity in a context of ever increasing richness, or should they evolve scientifically in unison with the context?

SCIENCE IS ALSO BECOMING INCREASINGLY GLOBAL. IN ANY MAJOR SCIENTIFIC MEETING, ONE SEES A HEALTHY MIX OF SCIENTISTS FROM ALL OVER THE WORLD. LIKEWISE, IN ANY MAJOR SCIENTIFIC JOURNAL, ONE SEES THE SAME RICH MIX OF SCIENTIFIC CONTRIBUTIONS. WHAT PURPOSE THEN WOULD NATIONAL AND CONTINENTAL (E.G., ASIAN, EUROPEAN, NORTH AMERICAN, LATIN AMERICAN, ETC.) SCIENTIFIC MEETINGS AND JOURNALS SERVE?

Response: All of us humans belong to local, regional, national and supranational communities. All of us aspire to recognition,

but few achieve it at national and international levels. Local and national meetings have, I feel, at least three significant roles to play. First, they offer recognition and encouragement to scientists of moderate visibility. Second, they create and maintain lively scientific ties among neighbors. Third and most importantly, they are training grounds and springboards for junior scientists, allowing them to gain expertise and confidence.

HOW HAS YOUR PHILOSOPHY OF EDUCATING GRADUATE STUDENTS/POSTDOCTORAL FELLOWS BEEN CHANGED OVER THE YEARS?

Response: Until I read this question, I wasn't aware having a philosophy of educating junior colleagues. Well, perhaps I do by trying to be with them as my mentors were with me. This means favoring the conditions for independent and gratifying research, offering thoughtful but not intrusive guidance, instilling persistence but not stubbornness, being expectant but not demanding. As an army officer, I was tought to "Command, Control and Correct" (the 3 "C"). As supervisors, we should try to "*Induce*, *Instruct* and *Improve*". This more than often works very well—but there may be the occasional exception when one also needs to *Insist*. Failure is the outcome when such a need persists.

This is how I see my attitude, and it has not changed much over the years. Perhaps there is now a touch of parental attitude, given the widening generation gap. Also, a specific aspect of the students' education to which I give increasing importance is the art of communicating, and mainly of writing. I have recently commented on the responsibility of educators to instil competent scientific writing (7). This requires time and patience, but the electronic age is not an excuse for sloppy writing. Everybody should be aware of the very wide difference between a scientific paper and a casual E-mail message.

WHAT WOULD BE YOUR ADVICE TO OUR JUNIOR PHARMACEUTICAL SCIENTISTS WHO ARE ABOUT TO EMBARK ON THEIR CAREERS?

Response: Based on the above, I would advice junior pharmaceutical scientists to keep their eyes wide open. By this, I mean to remain alert to unexpected findings, to observe what others can't see for lack of adequate mental agility or categories, and to retain a sense of awe. This obviously applies to all of us juniors and seniors. However, like the gift for languages which is common to all children and gone in many grown-ups, the fresh vision of many junior scientists tends to be progressively obscured by the non-scientific components of our careers. In a preface published some years ago, I use a meaningful verse by T. S. Eliot (8) to make this point. Its currency is not about to change.

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

Response: Senior scientists are the repository of their institution's collective memory, they have experience and a broad vision, and they can draw from a wider context. Junior scientists will tend to be more adventurous and to explore unconventional issues. Despite the schematic and even slightly caricatural character of these statements, the complementarity between junior and senior scientists is clear. So if I dare give only one piece of advice to my peers, it is to allow this complementarity to operate in full and develop into a genuine synergy. In practical terms, this means that the conditions must be right for senior and junior scientists to act as full partners, each contributing their best qualities. And since senior scientists often hold authority, it is their mission to set up such cooperative conditions.

DO YOU FEEL THAT WE ALL HAVE AN OBLIGATION TO PROVIDE VOLUNTEER SERVICE IN SCIENTIFIC ORGANIZATIONS OR, LIKE YOURSELF PRESENTLY, TO PROVIDE HIGHER ACADEMIC SERVICE IN OUR OWN HOME INSTITUTIONS?

Response: To provide volunteer service cannot be an obligation, but it may be a priviledge. All us us scientists have our own and private reasons for being interested in or indifferent to volunteering.

WHAT IS THE PLACE FOR ENTREPRENEURSHIP IN ACADEMIA?

Response: Bluntly stated, the less the better.

ACKNOWLEDGMENTS

I am very grateful to have been given this opportunity to make public some of my views and beliefs.

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