Nicholas Bodor. A Chemist from Transylvania in the American Chemical Society's Hall of Fame

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Most contributions of chemists to Medicinal Chemistry consist in discovering or inventing one or several new medicinal drugs. Very few chemists open up new methods for finding many medicinal drugs; Professor Nicholas Bodor (Nick to his friends) is such a chemist.

He was born in Satu Mare on February 1, 1939 in a family of Hungarian ethnicity. On the paternal side one can trace the roots of his Transylvanian family to the 14th century, and to the 16th century on the maternal side. From early childhood he showed exceptional qualities. He started school when he was 5 years old, two years ahead of all his classmates, and graduated first in his class at the age of 15. Based on a tough competition (180 candidates for 20 places), he was accepted in 1954 as a 15-year-old student to a five-year program as a Research Chemist at the Chemistry Faculty of the Bolyai University. All his studies had been in the Hungarian language, but in 1959 when he graduated as an organic chemist with an exceptional *red diploma*, Ceausescu's chauvinistic dictatorship closed the Bolyai University, unifying it with the Romanian counterpart (Babes Bolyai University) and discontinued courses in Hungarian.

As a result, Nick lost the promised academic position at the Bolyai University and started to work at a factory producing enameled products (dishes, stoves, etc.) in Satu Mare. He went through hard training to be an industrial engineer. In 1961, however, he was accepted at the Chemical Pharmaceutical Research Institute in Cluj (CPRI-Cluj), a subsidiary of the main Institute in Bucuresti. Because he wanted to continue his studies, he had to be accepted to the Russian-modeled doctorate (*aspirantura*). At that time, there were only two professors with the right to train aspirantura students in organic chemistry — professors Costin Nenitzescu and Eugen Angelescu, both in Bucuresti (nobody had this right in Cluj). Nick was accepted by Professor Angelescu at the end of 1961 (mainly due to the rare *red diplom*a and a personal interview), while he was still working full time at the CPRI-Cluj. Soon afterwards Professor Alexandru Silberg, who taught organic chemistry at the Babes Bolyai University in Cluj, received the right to supervise doctoral students and he became the new supervisor for Nick's doctoral research. After having finished with the mandatory oral examinations in a year, he started working on the research project, a subject he himself had selected (Isonitrosation of Substituted Nitrobenzenes, Application of the Hammett-Taft Equation) and approved by the new supervisor. Soon afterwards, quite fortunately, the Soviet-style aspirantura was converted into an Academy doctorate. At the research institute Nick had a very heavy workload. He was supposed to work only seven hours a day because of *dangerous work*. — and it was indeed, as they did not even have fume hoods. Thus, he would check out at 2:00 p.m. and immediately checked-in to start his thesis work. He worked alone every day until about 10:00 p.m. The research progressed smoothly and by 1964 he had typed (in the Romanian language) the Doctoral Thesis and the 50-page summary. The summary was sent out to some 100 selected chemists in the country. The rule was to have three Committee Members/Reviewers; two of the three had to be members of the Romanian Academy; all three had to be from different institutes in different cities.

Thus, as one of the three referees, I met Nick for the first time and this is how our friendship started. He defended his thesis (in Romanian) in January 1965, and the title *Doctor in Chimie* was approved in unanimity. The process continued with further review at the Romanian Academy of Science, and then by the Supreme Committee of Scientific Titles (such tight controls existed because at that time in Romania a significant monthly stipend was paid in addition to the salary for those who heldthe degree).

At the CPRI-Cluj Nick was responsible for many, mostly synthetic, projects. He published his first paper in 1964 in *Rev. Roumaine Chim.* in English [1] demonstrating a novel mechanism (opposite to the published work by the Syntex group) of direct iodination of 20-oxopregnanes, followed by four papers based on his thesis. However, in addition to the multiple synthetic chemical work, he was also interested in the theoretical and mechanistic aspects of organic chemistry. He was fascinated by Derek Barton's *Conformational Analysis* (Nobel Prize work) and the six brilliant papers published by M. J. S. Dewar in *J. Am. Chem. Soc.* on *The electronic basis of organic chemistry.* Nick wrote a few papers on the *Remote Effects* that had been discussed by Dewar in one of his papers. Nick did not like the demonstration of separation of substituent effects and provided an alternate proof. He sent the manuscript to Michael Dewar, who subsequently invited Nick to work at University of Texas in Austin, offering to him an R. A. Welch postdoctoral fellowship. When he asked for permission to leave, the authorities in Romania did not reply. However, due to the 1968 uprising in Czechoslovakia, he was provided an opportunity through some influential friends to be allowed to go to the University of Texas. However, he had to promise though to return in one year, which he did. Working with Michael Dewar was very rewarding and successful. Nick arrived in Austin in November 1968 and by February 1969 a joint paper was submitted to be published in *Tetrahedron* [2]. After his return to Romania, Michael Dewar invited Nick again, and he joined him in Austin in 1970. This time he did not return to Romania, and was thus sentenced *in absentia* according to the standard procedure for *defectors from the socialist regime*. Michael Dewar's semiempirical computational methods for organic substances based on molecular orbital

quantum-chemical parameters determined from empirical data were in full development [3]. In two years, Nicholas Bodor and Michael J. S. Dewar published eleven joint papers, mostly in the *Journal of the American Chemical Society*. Nick also published several papers without Dewar but with other post-doctoral students of Dewar such as Nenad Trinajstiæ from Croatia, or with Emil Pop from CPRI-Cluj, in Romania.

During this period Nick met and married Sheryl, his wife for 45 years. In order to take care of his family, Nick had to move to a different position. He accepted an offer from Professor Higuchi (University of Kansas at Lawrence, Kansas), who had started a research company, INTERx. This main job was to invent new *prodrugs* (a misnomer – predrug would be a better name for a molecule that after administration changes to an improved structure by a chemical reaction, possibly due to enzymes at the desired site). After one year he was promoted to Director of Research. In this position he authored some 70 patents and numerous publications (about 50), including his first *Science* paper [4].

In 1978 Nick was approached by the new Dean of the College of Pharmacy at the University of Florida and offered a position there as a Full Professor (a rare occurrence for a young researcher) and subsequently in half a year was named Chair of the Department of Medicinal Chemistry. He is now a Graduate Research Professor Emeritus (active) at the College of Pharmacy, University of Florida (UF) in Gainesville. In 1979 Nick received the first of a long line of NIH Grants. He built a group of coworkers that at some point consisted of up to 75 members of vastly different backgrounds. More than 50 doctoral students and more than 100 postdoctoral fellows were trained by him. He is also Executive Director of the College's Center for Drug Discovery that he founded in 1986.

Here one needs a brief digression for describing the concepts of *synthon*, and *retrosynthetic (or disconnection) approach*. At present, about 100 million chemical structures are known and recorded in the *Chemical Abstracts Service* (CAS) of the American Chemical Society, the vast majority of these are organic compounds obtained in the search for new medicinal drugs. Up until the 1970s, in order to find whether a chemical structure was new, one had to spend days in the library leafing through *Chemical Abstracts Indexes* and looking at possible IUPAC names for the particular isomer with the analytically found molecular structure. Nowadays, this only takes minutes thanks to chemical applications of graph theory that deal with molecular graphs (hydrogen-depleted graphs with vertices for atoms and edges for covalent bonds). The graphs have to be assembled directly on the computer screen with the CAS SciFinder Program. Thus, without words or names, the structure is directly found and chemistry is thus the best documented science. Of course, when using words, chemistry is not different from other sciences. Molecular graphs can be cut in various ways, and computer programs first introduced by E. J. Corey (1990 Nobel Prize for Chemistry) show all possibilities for the assembly of smaller units (*synthons*) into a target molecule – this is the r*etrosynthetic (or disconnection) approach*.

In the late 1970s Nicholas Bodor applied a similar concept that includes enzyme-catalyzed reactions occurring in living cells, and invented the retrometabolic drug design system [5]. It is based on the mechanism of drug action in various tissues and it aims at improving the therapeutic index and diminish unwanted side effects. It combines two complementary concepts, namely (i) *chemical delivery systems* (CDS) with (ii) *soft drugs* (SD). In general*, a CDS is inactive* by design and is enzymatically *activated* stepwise to produce the active drug *only* (or preferentially) at the target site/organ. At the other end of the retrometabolic design loop are the soft drugs. A *SD is an active drug,* designed in such a way to be *deactivated* in a predictable and controllable way after it achieves its therapeutic role. One method of the soft drug principles of Dr. Bodor is to apply the *inactive metabolite approach.* According to this, the design starts with an inactive metabolite of a known drug which is then chemically modified (activated) to produce an isosteric/isoelectronic analogue of the active drug which then, when applied at the site of need, will perform the desired function. However, when it is absorbed or reaches the systemic circulation, it will be deactivated to the very inactive metabolite the design started from. By design this deactivation takes place by hydrolytic enzymes and avoids the usual oxidative metabolic processes. On the other side of the retrometabolic drug design loop are the CDSs. A striking example for a CDS introduced by Bodor is the *brain targeting of drugs* based on a redox targetor system, such as 1,4-dihydrotrigonelline↔trigonelline salt. The structurally similar, ubiquitous $NAD^+ \leftrightarrow NADH$ redox coenzyme system assures oxidation of the initial lipophilic drug targetor conjugate to the hydrophilic, inactive quaternary form, which is due to the unique architecture of the blood-brain barrier (BBB), is *locked-in* the brain, but is eliminated fast from the whole body. Thus, further enzymatic liberation of the drug takes place essentially only in the brain, in a sustained manner. The first successful brain delivery-targeting of neuropeptides was accomplished by Bodor by combining the above redox targetor system with strategically selected amino acid *spacers* and large lipophilic modifiers, called *molecular packaging* undergoing *sequential metabolism*, a general method applied now to a variety of neuropeptides, which was highlighted by the *Harvard Health Letters* as one of the top ten discoveries of 1992. Other types of CDSs invented by Dr. Bodor target drugs to the eye, to the lungs and to specific receptors.

Among hundreds of drugs found worldwide through Nick's methodology and his computerized expert system, one should mention the soft drug Loteprenol Etabonate, an ophthalmic corticosteroid invented by Nick that is used in suspensions against eye inflammation (for instance, after cataract surgery) and allergic diseases. It was approved in 1998 and is sold in five different products. It is one of the most important and safest eye drugs. Another eye-specific drug invented by Nick is betaxoxime, which is inactive when administered but becomes active in eyes after converting, by design, an oxime into a ketone function, followed by its stereospecific reduction.

Nick organizes the biennial Retrometabolism Based Drug Design and Targeting Conference. In addition to Florida, meetings in this international series have also taken place in Japan, Hungary and Austria. He has authored or co-authored 520+ papers and over 200 patents. More than half of these patents were assigned to the University of Florida.

The first two companies that he founded were Pharmatec (which went public in1985) and Xenon Vision in1986, both with participation of the University of Florida. In 1999 he accepted a position at IVAX Corp., a world-wide pharmaceutical company (some 12,500 employees) as its Chief Scientific Officer. He was for several years President of the IVAX Research Institute, Inc. and Managing Director of the IVAX Drug Research Institute in Budapest, Hungary (formerly the Central

Pharmaceutical Research Institute of Hungary) with a leave of absence from the University of Florida. After IVAX merged with Teva in 2006, he returned to UF and additionally started Bodor Laboratories Inc. where he works today with both his son Erik and daughter Nicole to continue development of his new technologies. One current project focuses on Sofpironium Bromide, a soft anticholinergic invented by Nick with unique structure and properties which has recently shown success in a Phase IIb study for the treatment of hyperhidrosis, a medical condition with significant unmet needs.

Nicholas Bodor has been honored by numerous awards, among which are:

- Member of the Hungarian Academy of Sciences (1995)
- Fellow of the American Academy of Pharmaceutical Sciences (1983)
- Fellow of the American Association of Pharmaceutical Scientists (1986)
- Fellow of the American Association for the Advancement of Science (1989)
- Fellow of the American College of Clinical Pharmacology (1991)
- Honorary Member of the Panhellenic Society of Pharmacists (1989)
- Fellow of the International Nagai Foundation Tokyo (1995)
- AACP Volwiler Research Achievement Award (1997)
- AAPS Distinguished Pharmaceutical Scientist Award (2007)
- Florida Scientist of the Year (1984)
- Doctor Honoris Causa, University of Florida (2005)
- Doctor Honoris Causa, Technical University of Budapest (1989)
- Doctor Honoris Causa, Medical University of Debrecen (1990)
- Fabinyi Prize of the Hungarian Chemical Society, given to eminent scientists living outside Hungary (2010)
- Gold Cross of Merit of the Hungarian Republic (2004)
- Commander's Cross of the Order of Merit of the Hungarian Republic (2010)
- Hall of Fame of the American Chemical Society (2012)

In addition, a Distinguished Professorship named the *Nicholas Bodor Professor in Drug Discovery*, was established at the University of Florida in 2007. Furthermore, a Nicholas Bodor Distinguished Lectureship was introduced in 2014.

Dr. Emil Pop, who had been his fellow researcher at CPRI-Cluj, was invited by Nick to Gainesville, Florida, to work first at the University of Florida and then at Pharmatec/Pharmos as Director of Chemistry. Later, Nick helped Dr. Pop to established his successful synthesis company, Alchem Corp. (Dr. Pop passed away recently). For about the last 15 years, Professor Bodor has also supported two scholarships at two high schools in Romania, his alma mater in Satu Mare and at the Bolyai College in Tirgu Mures, awarding annually a diploma and significant monetary support to the best student in chemistry.

I believe that Professor Nicholas Bodor's remarkable activity deserves to be better known and appreciated by Romanian chemists.

References

1.N. BODOR, L. FEY, M. KIRCZ AND F. HODOSAN, On Direct Iodination of the 20-Oxopregnanes, Rev. Roumaine Chim., 9, 147 (1964).

2.N. BODOR AND M. J. S. DEWAR, Ground States of Sigma-Bonded Molecules. VIII: MINDO Calculation for Species Involved in Nitration by Acetylnitrate, Tetrahedron, 25, 5777-5784 (1969).

3.M. J. S. DEWAR, A Semiempirical Life, Am. Chem. Soc., Washington, D.C., 1992.

4.N. BODOR, E. SHEK AND T. HIGUCHI, Delivery of a Quaternary Pyridinium Salt Across the Blood-Brain Barrier by Its Dihydropyridine Derivative, Science, 190, 155-156 (1975).

5.N. BODOR, P. BUCHWALD, Retrometabolic Drug Design and Targeting, Wiley, Hoboken, New Jersey, 2012.

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