The meeting of minds and times with Peter Riederer: an appreciation

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"The harder you work, the harder it is to surrender."  
Vince Lombardi

It is fair to say that if I had not received a phone call at Oxford University from Prof. Merton Sandler in summer of 1973, that a young chap by the name of Peter Riederer, from Prof. Walter Birkmayer Department, was in London and wanted to discuss some aspects of monoamine oxidase (MAO) inhibitors for Parkinson’s disease (PD), I probably would not be where I am today. If there were two contrasting people, that were us. Here was this large but soft spoken, rather gentle and austere Viennese, meeting a small rather assertive individual from Iran. It was meeting of the minds and an instant connection that has lasted some 34 years, with a result of some near one hundred joint publications, some 25 books and hopefully advancing the prospect for treatment of PD. Peter wanted to know was there an MAO inhibitor that did not cause a “Cheese Reaction”, a side effect of first generation of non-selective MAO inhibitors, that could be employed in the treatment of PD. In 1961 Birkmayer and colleagues had used MAO inhibitors to treat PD, gastrointestinal and blood pressure problems in such patients was a limiting factor. My instant reaction to his request was that the Hungarian pharmacologist, Joseph Knoll, whom I had met at the MAO meeting in Sardinia in 1971, in honour of Hugh Blaschko, had described a failed MAO-B inhibitor anti-depressant called L-deprenyl, that did not give a cheese reaction in isolated pharmacological preparations and in vivo (Knoll and Magyar, 1972). The other logic of using L-deprenyl was that in 1970 with Merton Sandler we had studied MAO activity in different human brain regions (Collins et al., 1970; Youdim et al., 1972). The basal ganglia, had a higher activity towards the MAO-B substrate benzyamine and dopamine than the other regions, suggesting that predominance of MAO-B in this brain region. It was decided I should stop over in Vienna to give a lecture on MAO for Birkmayer sake, since I was going to meet Joseph Knoll in Budapest, and present a paper at the Hungarian Pharmacology Society.

I had once before been in Vienna as a stop over, but this time Peter was a great host. After the lecture at the Neurological Institute we landed in a Heurige restaurant, drinking a significant amount of the young wine and thinking that the Hungarians might have a gold mine in L-deprenyl that they were not aware of. The ensuing headache that evening was worth what was to come eventually with L-deprenyl. Peter explained to me why he was looking for an MAO-inhibiting substance without major side effects and we decided to convince Birkmayer to try L-deprenyl in parkinsonian patients with on–off-phases. I let have some 5 mg of L-deprenyl, which I had received from Joseph Knoll in Budapest and transferred to Peter Riederer and Birkmayer at a lunch in the Sacher restaurant in Vienna, with the emphasis that if it should cause hypertension in the PD subject, we should abandon the project. Later Joseph Knoll did not appreciate our hypothesis about the usefulness of L-deprenyl as dopaminergic drug for PD, when I told our intention. He insisted that that L-deprenyl acted as psychoenergizer like amphetamine with phenylethylamine being its major action. Some months later at Oxford our secretary informed me that I have a call from an excited person by the name of Riederer from Vienna. My first reaction was that the use of L-deprenyl by Birkmayer has had a major side effect in PD subjects. But Peter assured me that L-deprenyl was given to 44 PD subjects and the drug works (Birkmayer et al., 1975, 1977; Lees et al., 1977).
The lack of video in those days resulted in making a film of some of the patients. The clinical results were presented at the 5th International Congress of PD in Vienna and Melvin Yahr, who was the second investigator to study L-deprenyl, asserted in the summary of the congress that this is a novel new direction for the treatment of PD (Yahr, 1975). The rest is history except that it took nearly 15 years before L-deprenyl, renamed in USA as selegiline, reach its shores.

The next stage in this collaboration was the long term effect of L-deprenyl, which we (Birkmayer et al., 1983, 1985) had studied in more than 800 subjects since in 1975. It was apparent that L-deprenyl as adjuvant to L-DOPA (L-3,4-dihydroxyphenylalanine, levodopa) may alter the progression of the disease and we wrote in the summary of the paper presented at the MAO meeting in Heidelberg “The prolongation of the evolution of Parkinson’s disease with long-term (−) -deprenyl treatment shows for the first time that the degeneration of the dopaminergic nigrostriatal fibers can be depressed to some extent” (Birkmayer et al., 1983). This was prior to the identification of MPTP (N-methyl-4-phenyl-1,2,3,6-tetra-hydropyridine) as a dopaminergic neurotoxin and its prevention by L-deprenyl in 1984 (Heikkila et al., 1984). The rest is history resulting in the publication of thousands of publications on various aspects of L-deprenyl, pharmacology and neuroprotection. It also led to the development of a number of other MAO-A and B inhibitors as anti-Parkinson drugs by many pharmaceutical companies, which all failed to reach the market. The exception being rasagiline (Azilect®) a restricted analogue of L-deprenyl, which John Finberg and I co-developed with Teva Pharmaceutical Company (Youdim et al., 2005).

The other aspect of our collaboration has been the work we initiated on brain iron metabolism in PD, a subject I started at Oxford in 1974, at the time when no one had paid much attention to the role of iron in brain function and dysfunction (Youdim, 1985). It was Sheila Callender, the Reader in Department of Haematology at Oxford University who had read one of my earlier papers on iron metabolism and MAO and asked why I had not continued the work on brain iron metabolism. As a consequence my group started the work on brain iron metabolism, which was presented at the Ciba Foundation symposium (Youdim and Green, 1976) and summarized in the Handbook of Neurochemistry (Youdim, 1985) with some emphasis on role of iron in oxidative stress and PD. 1985 was another turning point for Peter and I when we met at the International Society for Neurochemistry in Copenhagen, where Paul Mandel had invited me to talk about iron and brain function. The subject of human brain iron metabolism came up, I imparted to Peter that several publications from 1924 and 1968 had shown that iron is increased in substantia nigra of PD and this could be relevant to the pathology of the disease. His response was that he had similar data and which were presented at meeting in Austria in May 1985, well before the published letter of Dexter et al. in the Lancet (1987). So for the second time we had the meeting of the minds to explore the role of iron in PD and that led to extensive collaborations and publications on brain iron in PD and its animal models, which has now become a major topic of interest in neurodegenerative processes and other neurodegenerative diseases, including Alzheimer’s disease (Riederer et al., 1989; Gerlach et al., 1994; Berg et al., 2002, 2004; Götz et al., 2004; Zecca et al., 2004). This topic led to my collaboration with Avraham Warshawsky in 1989 for the development of brain permeable iron chelators as therapeutic agents for PD and other neurodegenerative disorders including Alzheimer’s disease, which we have done very successfully (Youdim et al., 2004; Gal et al., 2005; Zheng et al., 2005a, b), demonstrating that iron chelators are neuroprotective in 6-hydroxydopamine kainate and MPTP models of PD.

The collaboration with Peter did not weaned there and took another turn when we decided to study the mechanism of dopamine neurodegeneration in the MPTP model of PD and in sporadic PD brains employing for the first time transcriptomics and proteomic profiling of substantia nigra pars compacta. With out Peter’s ability to obtain PD brains from the brain banks in Austria and Germany this project would have never have got of the ground and it was the first time that this approach was made for the study of sporadic PD. I consider this as probably the most important and significant work we done, since it brings a new dimension to the study of neurodegenerative processes in PD and opens up novel avenues on the mechanism of neurodegeneration, novel drug development and even development of phenotypic model of sporadic PD (Grünblatt et al., 2004; Mandel et al., 2005).

The meeting of the minds between Peter and I was not directed entirely in our research interests. It included exchange of students, post-doctoral fellows, organization of numerous symposia, conferences and congresses and editing of many books and traveling to all corners of the world and presenting the results of our collaboration.

Above all these events, there is the human side of Peter Riederer as a friend, colleague and teacher. His humanity can be measured by the constant support he has given to his colleagues, the young students, Israeli scientists, Israel and myself. He is the only person who has never failed to visit Israel, to participate in conferences and support it no matter if there was a conflict in Israel with its Arab neighbors.