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Oxidative Stress and Neuroprotection

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My love with monoamine oxidase, iron and Parkinson's disease

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I had intended to go to medical school and was accepted to McGill University, Montreal (1959). During my preclinical B.Sc (1961) degree, the courses of biochemistry and neurochemistry were to influence me so much that I gave up the idea of medicine and decided to take a Ph.D in neurochemistry-neuropharmacology and was directed to Theodore L. Sourkes, at the Allan Memorial Institute (McGill University Department of Psychiatry), who was working on monoamine oxidase (MAO), MAO inhibitors, serotonin, depression, dopamine and Parkinson's disease. Ted, as he is affectionately known to all his colleagues, accepted me for an Msc. and Ph.D where I started to work on serotonin metabolism and MAO. In my M.Sc thesis I provided one of the first physico-chemical and pharmacological evidence for two forms of MAO in rat liver and brain mitochondria, which have now been shown to be two separate proteins (MAO A and MAO B). I presented these data at FASEB meeting in Atlantic City (1963), where I met Menek Goldstein and Toshi Nagatsu who remained my close friends ever since and the chairman was Albert Zeller, the discoverer of first MAO inhibitor, iproniazid. For my PhD I decided to purify MAO. After two years we eventually were able to solubilize and purify MAO. We showed that the purified enzyme still exhibited two forms of MAO with different inhibitor sensitivities. In 1966 I went back to England to continue my work on MAO and its multiple forms with Merton Sandler, where I remained until 1972 as a Welcome Research Fellow. These were to be some of my formidable years. It was while with Merton Sandler that I met Keith Tipton with whom I forged a friendship and collaboration that remain until today. With Merton Sandler, in a series of papers published in Nature, we described the multiple forms of MAO in rat and human brains and showed that human basal ganglia contains mostly MAO B. This finding was to have a major impact later on in the treatment of Parkinson's disease with MAO B inhibitor l-deprenyl (selegiline). We also showed for the first time the effect of selective MAO A (clorgyline) and non selective MAO inhibitors (tranylcypromine, isocarboxazide) on MAO and amine metabolism in human brains, obtained at autopsy from geriatric subjects with terminal diseases treated with MAO inhibitor antidepressants. In the Nature paper (Youdim et al. 1972) we predicted the future development of selective MAO inhibitors directed at each enzyme form as antidepressants, but devoid of their major side effect, namely potentiation of sympathomimetic action of indirectly acting amines (tyramine), known as the ''cheese reaction'' (which eventually led to the development of reversible MAO A inhibitor antidepressants such as moclobemide and brofaromin. In 1972 Jacques Glowinski invited me to spend a year at College de France in Paris as Welcome Trust Fellow, and with Michel Hamon we purified tryptophan hydroxylase and during which time I met Hasan Parvez as consequence being his Ph.D examiner. While in Paris David Grahame-Smith offered me a position at the MRC Unit and Department of Clinical Pharmacology at Oxford.

The four years (1973–1977) I spent at Oxford was to profoundly change my carrier. The department consisted of a dynamic group of young individuals (A. R. Green, F. Woods and J. Aronson, and David Boulin) with different talents who wanted to succeed badly. Thanks to Grahame-Smith, the department and its members achieved world

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prominence. Here I continued to study the physiological roles of MAO A and B. Specially MOA-B, with highest encouragement from High Blaschko, who was at the department of pharmacology. Blaschko, never failed to support me and was responsible for me to come to Oxford. Within the first year at Oxford I meet two individuals who influenced me so much, that if I had not met them, my carrier would certainly have taken a different turn. The first was the hematologist Dr. Shiela Calendar, Reader in the Department of Medicine at Oxford. She had read an earlier paper of mine on iron and MAO from my years with Ted Sourkes and thought why I had not continued my studies on brain iron metabolism and neurotransmitter metabolism. The reason being that nutritional iron deficiency was the major nutritional deficiency in the world affecting 4–600 million individuals and iron deficient children have abnormal behavior and cognitive defect. Iron is a cofactor of the major enzymes of the mitochondrial electron transport system and for synthetic and metabolic aminergic neurotransmitter enzymes (tyrosine hydroxylase, tryptophan hydroxylase and monoamine oxidase). An abnormality in serotonin, dopamine and noradrenaline might explain the altered behavior in the iron deficient children. Practically there were no published works on brain iron distribution, regulation, metabolism had been done. I set up a rat model of nutritional iron deficiency with Richard Green and showed it resulted in reduction of brain iron metabolism and diminution of aminergic (serotonin and dopamine) neurotransmission and behavioral responses. In retrospect we were among the first to suggest that dopamine sensitive adenylate cyclase was not the dopamine receptor, since in iron deficiency this enzyme and its response to dopamine was not changed in the striatum. Yet the behavioral response of iron deficient rats to amphetamine and apomorphine were almost completely diminished. We suggested that either dopamine sensitive adenylate cyclase is not the receptor or that iron deficiency affects some component after adenylate cyclase. Indeed when the radio ligand (haloperidol and spiperone) were identified by S. H. Snyder to bind to dopamine D2 receptor, we examined these receptors in the striatum of iron deficient rats and showed that they are decreased which explained the dopaminergic subsensitivity and the reduction in apomorphine behavioral responses (Ben Shachar et al.). These studies have continued to receive world wide recognition from WHO, pediatritions, nutritionists and neurologists.

The second individual, who was to have the greatest impact on my carrier was meeting Peter Riederer for the fist time in Nov./Dec. 1973 in London and again in Vienna in early 1974. Another influencial person was Alfred Pletscher who believed in MAO inhibitors as therapeutic agents and invited me to my first CINP Congress in Paris. The association with Peter has been one of the most fruitful and productive period that is still on going. He was a member of Prof. Walther Birkmayer's, Neurology Department at Lainz Geriatric Hospital, Vienna. Peter wanted to know whether there was any new MAO inhibitors without ''cheese reaction'' he could use in Parkinson's disease as adjuvant to L-dopa. Some years earlier (1961) Birkmayer and Oleh Hornykiewicz had employed iproniazid, nardil and nialamide with L-dopa in parkinsonian subjects. Although the beneficial effects of L-dopa were potentiated, severe side effects were observed. Peter and I decided that MAO-B inhibitor l-deprenyl was the choice since it did not produce a cheese reaction as reported by Knoll and Magyar and dopamine was equally well metabolized by both MAO-A and B in vivo). On a visit to meet Joseph Knoll in October of 1974. I was able to get 5 gm of l-deprenyl and a study in 47 Parkinsonian patients by Walther Birkmayer in Vienna could be immediately related. Its success was reported at 5th Congress of Parkinson's Disease in Vienna (1975). Eventually other neurologists became aware of l-deprenyl and among the first was Melvin Yahr and l-deprenyl became one of the major innovative antiParkinson drugs. The other reason why L-deprenyl received such prominence was the description of our data in 1983 and 1985 pointing to its possible ability to slow down the degeneration of nigrostriatal dopamine neurons in Parkinsonian subjects. This was the first time the concept of ''neuroprotection'' and retarding the neurodegeneration of nigrostriatal dopamine neurons was discussed. L-deprenyl and MAO-B inhibition received further prominence as consequence of the discovery of the human inducing parkinsonism by the synthetic neurotoxin MPTP (N-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) resulting from the observation that MPTP was a substrate of MAO-B and l-deprenyl pretreatment prevented its neurotoxicity in vivo and cell culture. This led to a floury of pharmaceutical companies developing MAO-A and MAO-B inhibitors, the presumption being that Parkinson's Disease is consequence of an environmental or endogenous factor similar to MPTP. Non of these MAO inhibitors survived into the clinic, except moclobemide (reversible MAO-A antidepressant) and rasagiline (to be discussed later). By this time l-deprenyl was in European clinics and did not reach USA until 1989, some fifteen years later from our first publication, named selegiline.

At Oxford together with Gretel Holzbauer, Hasan Parvez and Simmone Parvez we extended the work started by Margaret Southgate and Merton Sandler on hormonal reg-

ulation of MAO-A and B and the profound effect oestrous cycle has on brain MAO activity, specially in the hypothalamus and striatum.

It was in on the occasion of International Neurochemistry Society meeting in Copenhagen (1978) that Peter and I came up with the concept of ''iron, radical oxygen species and oxidative stress roles'' in neurodegenerative aspect of Parkinson's disease. The basis of it was laid down in a paper I presented at the Iron Symposium, which I had organized with Alan Jacobs (Professor of Hematology at Cardiff University) in 1976 at Ciba Foundation in London. I had reviewed the human and animal brain iron metabolism in relation to work with Richard Green on the effect of nutritional iron deficiency on aminergic neurotransmission. I came across several papers from 1920's by Spatz that distribution of iron was uneven in the brain, with the highest being in globus pallidus, substantia nigra, red nucleus, detate gyrus and thalamus, with most of brain iron being found in extrapyramidal regions. What puzzled me are papers by Lehermitte et al. (1924) and Earle (1968) that iron is increased in substantia nigra of Parkinsonian brains as compared with matched controls. With Peter we decided to re-examine brain iron in Parkinsonian brains subjects and its implication for oxidative stress induced neurodegeneration. Peter had analysed iron and other elements in a pilotstudy in controls and PD brain areas already in 1976 and 1977 based on work published by Ule and his group in 1972 and 1974 on the age-dependent distribution of iron in the ''normal'' brain. These date were presented at the 75th birthday symposium for Walther Birkmayer in 1985 and published in the thereof proceedings. In 1989 we published our work on a summary of iron and oxidative stress related parameters in J. Neurochem. and showed that iron was increased, GSH and ascorbate were decreased in substantia nigra, the implication being that iron induced oxidative stress may have a pivotal role in dopaminergic neurodegeneration with confirmation coming from other laboratories. We went on to show that indeed iron was increased in those melanin containing dopamine neurons of substantia nigra that selectively die. Furthermore similar events occur with 6-hyroxydopamine and MPTP. I demonstrated for the first time that iron chelators (desferal and Vk-28) can prevent the neurotoxicity of these neurotoxins. This led to suggest brain permeable iron chelators as therapeutic approach to PD a concept confirmed by other groups and chelation therapy is now considered one approach to neuroprotection.

With Margaret Thatcher coming to power and the lack of available university position in UK, I decided to leave Oxford (1977) and was offered to set up the Department of Pharmacology in the newly opened Medical School at Technion in Israel. During the time at Oxford one of the great scientific pleasure was to visit Hugh Blaschko, when ever opportunity arose. We discussed many aspect of MAO-A and B functions. He was fascinated by our findings on the antiParkinson action of l-deprenyl. He advised me to concentrate on studying MAO-B many times, including the time I went to bid him good bye, before leaving UK. I clearly remembered that among the MAO inhibitors which we received, while with Sandler, were two compounds (AGN1133 and AGN1135) with similar structures to l-deprenyl. l-Deprenyl was the only MAO inhibitor known that did not give cheese reaction. The intriguing question was whether l-deprenyl had a specific pharmacological action that prevented the cheese reaction (as suggested by Knoll and Magyar) or that any MAO B inhibitor would do the same thing. By the time John Finberg joined my department in Haifa we had identified that AGN1135 was the second selective MAO B inhibitor and went on to show that it had pharmacological actions identical to l-deprenyl and that it did not produce a cheese reaction in animal and pharmacological preparations at its selective MAO-B inhibitory dosage. Further more unlike l-deprenyl it was devoid of sympathomimetic activity. Indeed it was John Finberg and Meir Tenne who established that the cheese reaction is the property of MAO-A inhibition within the adrenergic neurons and that when MAO-B is inhibited selectively, no cheese reaction would occur. As a consequence we were among the first to suggest development of MAO-A inhibitors with out the cheese reaction as antidepressant that led to my long association with Alfred Pletscher, William Haefely and Moshe Da Prada at Roche and led to the discovery of the first reversible MAO-A inhibitor, moclobemide, without the cheese reaction by Moshe Da Prada and others followed. These findings were the imputes for the development of other MAO-B inhibitors as antiParkinson drugs and reversible MAO-A inhibitors as antidepressant by some of the major pharmaceutical companies. It is ironical that non of those newly developed found their way into the clinic (except eventually moclobemide and rasagiline). Because AGN1135, unlike l-deprenyl, did not have sympathomimetic activity or be metabolized to amphetamine and was a potent MAO-B inhibitor, we suggested its development as anti PD drug. Eventually it was co-developed with Teva Pharmarmaceutical Co. and rasagiline (Azilect) has been approved for Europe and Israel and letters of approval have been received from FDA. This would not have been achieved with if it were not for the unflinching efforts of my colleague and friend Dr. Ruth Levy of Teva, who one day in came to my office back in 1987 saying they are interested to develop AGN1135 as

antiParkinson drug. Together with Makato Naoi, Wakako Maruyama and members of our Center (Tamar Amit, Silvia Mandel, Ori Bar Am, Orly Weinreb and Yotam Sagi) we elucidated the molecular mechanism of rasagiline's neuroprotective activity and showed that it was not dependent on its MAO inhibitory activity, but rather on the propargyl moiety, since the S-optical isomer of rasagiline, TVP 1022 and propargylamine are poor inhibitors of MAO, yet have the same molecular neuroprotective property with similar potency. The mechanism of these propargylamines results from interaction of Bcl-2 family protein with PKC-dependent MAPkinase pathway.

The conventional neurochemistry, genomic and proteomic profiling studies were demonstrating that neurodegeneration is associated with a cascade of events and failure of several neurotransmitter systems. The concept of targeting multiple disease etiologies that lead to neurodegenerative disorders (such as Alzheimer's disease, Parkinson's disease amyotrophic lateral sclerosis and stroke), is challenging the widely held assumption that ''silver bullet'' agents are superior to ''dirty drugs'' in drug therapy. Accumulating evidence in the literature suggests that a drug with two or more mechanisms of action targeted at multiple etiologies of the same disease, may offer more therapeutic benefit in certain disorders than a drug that targets one disease etiology only. In addition, such multiple mechanism/multifunctional drugs may exhibit a more favorable side-effect profile than a polypharmacology combination of several drugs that individually target the same disease etiologies than those identified for a single multifunctional drug. In the last few years in collaboration with Marta Weinstock (the developer of the antiAlzheimer drug, rivastigmine) we designed and developed several novel cholinesterase- brain selective monoamine oxidase AB inhibitor compounds (TV3326 and TV3279). These compounds were developed from the pharmacophore of rasagiline, its S-isomer and carbamate cholinesterase inhibitor moiety in order to possess the neuroprotective and MAO and cholinesterase inhibitory activities for treatment of AD subjects having co-morbidity with depression and Parkinson's disease. Ladostigil (TV3326) is a unique brain selective MAO-AB-cholinesterase inhibitor that in animal studies shows antiAlzheimer, antiParkinson and antidepressant activities, besides being neuroprotective and the ability to process amyloid precursor protein implicated in Alzheimer's disease. Ladostigil (Teva Pharmaceutical Co. Israel) is finishing its Phase II clinical studies. Another example of multifunctional neuroprotective drug that we recently designed and are under development are the iron chelator-brain selective MAO-AB inhibitors, M30 and HLA-20. In these drugs we have introduced a propargyl MAO inhibitory moiety at different sites in our brain permeable neuroprotective iron chelator, VK-28 which Avraham Warshawsky (deceased) and I developed in 1989 and Mati Fridkin took over the project successfully with our Ph.D student Hailin Zheng. Unlike l-deprenyl and rasagiline, which do not increase brain levels of dopamine, ladostigil and M30 does so, as consequence their ability to inhibit MAO-AB. Thus, they may represent more effective as drugs for PD. We have shown that these multifunctional propargylamine drugs have neuroprotective activity in vitro neuronal cell cultures, and in vivo models of Parkinson's disease, Alzheimer's disease and Huntington disease similar to rasagiline. An added bonus for the iron chelator-MAO inhibitor, M30, is its ability to prevent the neurotoxicity resulting from dysregulation of iron in MPTP, 6-hydroxydopamine and kainate treated animals and which has also been established at brain sites in the neurodegenerative disorders models, where neurons die. Our present efforts now are directed at determining the brain selectivity of ladostigil and M30 for brain MAO inhibition, which may allow us to synthesize further similar drugs.

More recently I have ventured back to studies on depressive illness specially in Parkinson's disease and mechanism of action of different classes of antidepressants including MAO inhibitors employing the technique of gene expression with cDNA microarray and proteomic profiling, the first group to do so. With this system we have identified how complex the mechanisms of antidepressant actions are and have identified a homology of 37 gene expressions with 5 different classes of antidepressants that may explain their common final pathway as antidepressants. The down stream gene pathways identified may lead to novel new drugs away from the classical MAO and amine up take inhibitors presently in the clinic.

In 2006 The British Pharmacology Society decided to celebrate its 75th Anniversary of the founding of Society, and the 60th Anniversary of the first issue of its Journal, BJP, the British Journal of Pharmacology. To commemorate these important anniversaries, BJP decided to publish a special supplement, comprising a series of articles by distinguished scientists who have been actively involved in areas of the subject in which British pharmacologists have made a contributions and major pharmacological discoveries of the past half-century. I was honoured and delighted that they chose the subject of monoamine oxidase and its inhibitors by including my contribution to the field (Youdim and Bakhle, 2006).

I wish to express my gratitude and thanks to all who a have contributed to this publication, which I consider

an honour, since there is no substitute to be recognized by ones colleagues. Special thanks to Peter Riederer and Hasan Parvez for organizing this volume and allowing me to give a biography of my 40 years love affair with MAO. Special appreciation and thanks to Keith Tipton for the long association, who never failed to support any suggestion I had and more recently for collaborating on the new MAO review, 40 years on to appear in Nature Review Neuroscience (Youdim et al., 2006) I have been lucky to have worked and collaborated with some of the finest scientific colleagues, with out whose collaboration, insights, efforts and patience I would not have achieved some of the goals I set for myself. As a consequence of space I have left out the names of many other colleagues and students who worked with me in other projects. Special thanks to them.

References

Youdim MB, Bakhle YS (2006) Monoamine oxidase: isoforms and inhibitors in Parkinson's disease and depressive illness. Br J Pharmacol 147 [Suppl 1]: S287–S296

Youdim MBH, Edmondson D, Tipton KF (2006) Therapeutic potentials of monoamine oxidase inhibitors. Nat Rev Neurosci 7: 295–309

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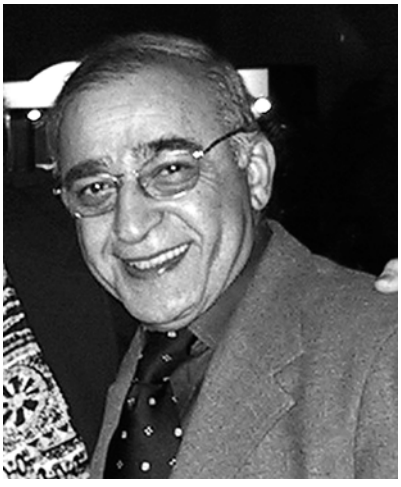
Preface
Moussa Youdim – an appreciation



It would be possible to write at considerable length about Moussa and still not do him full justice on his 65th birthday. Indeed, within the constraints of this brief appreciation, many things that might be said about the numerous awards he has won, his contribution as an editor of many journals, the books that he has edited etc., will have to be left out. Nonetheless, a brief resume of his career is important to illustrate his unique personality and achievements.

Born in what was formally known as Persia, and educated in England, he is reported to have said that during his studies he accepted the ''European lifestyle'' and never moved back. His career as a research scientist began in the Laboratory of Ted Sourkes at McGill University in Canada, where he gained his PhD in Biochemistry. There could have been few better places to absorb a passion for research allied with a rigorous and critical approach than in Ted's laboratory. It was there that he developed his dual interests in monoamine oxidases and the roles of iron in the brain, both of which were to play central roles in much of his subsequent research. He then relocated to England in order to work in the laboratory of Merton Sandler in Queen Charlotte's Hospital London where his interests in monoamine oxidase fitted in well with those of Merton's group. This, as well as the time he spent at Oxford where he developed collaborations with many other laboratories in the UK, notably that of David Graham-Smith and Richard Green in Oxford, proved to be a most productive period for him. He also spent an all-too-brief period working in my laboratory in Cambridge looking at MAO in the adrenal medulla-in addition to having a lot of fun. Whilst there he developed friendships with a scholar of ancient Persian Literature as well as with Sir Rudolph Peters, who among many other accomplishments, developed the concept of lethal synthesis and founded the journal Biochemical Pharmacology. More notably, he developed collaborations with Walther Birkmayer and one of us (P.R.) in Vienna, which led to the demonstration of the effectiveness of *l*-deprenyl (Selegiline) in the treatment of Parkinson's disease. This work attracted worldwide attention and led to an explosion of research and publications on deprenyl as a 'neuroprotective' drug and the revival of MAO inhibitors as antidepressants. His continuing collaboration with Peter Riederer also resulted in the further development of fundamental ideas about defects of iron homeostasis being an important contributing factor in the aetiology of neurodegenerative diseases.

In 1977 he was invited to set up a department of Pharmacology at the Technion Institute in Haifa. Although one does not normally find much good to say for the baleful bureaucrats who run many of our institutions, this was however, an admittedly inspired move on their part. Certainly England's loss was Israel's gain. In addition to getting the department organised, he continued his own research at an ever increasing pace with the able assistance of our collaborator John Finberg. At the same time he was extremely active at promoting Technion around the world and obtaining funding for its activities. He subsequently moved from the department to set up his own research centre within the Technion institute; a centre for neurodegenerative diseases research which now bears such a long name that it would exceed the allowable word count were I to give it in full

here. That notwithstanding, it is recognized as a Center of Excellence by the National Parkinson Foundation (USA).

He formed a collaboration with the gifted chemist Asher Kali, resulting in the synthesis of a range of novel monoamine oxidase inhibitors, including anti Parkinson's drug Rasagiline, which appears to have several advantages over Selegiline. It is not necessary to discuss the drugs merits here, since it has been the subject of many scientific and clinical publications, including the present volume of our Journal. It appears very likely that we will hear much more about Rasagiline and its efficacy in treating neurodegenerative diseases in the future.

His interest in bifunctional drugs that developed around this time resulted in his collaboration with Marta Weinstock. Their collaboration brought forth the synthesis of a compound, which contains monoamine oxidase and amine reuptake inhibitory functions in a single molecule and is indicated for the treatment of Alzheimer's disease. Although this compound was less effective than might have been hoped, the same approach resulted in the development of a series of drugs including combined iron chelator-monoamine oxidase inhibitor drugs and the cholinesterase-monoamine oxidase inhibitor, ladostigil. Both classes of bifunctional drugs show considerable promise and the outcomes of further studies are eagerly awaited.

Translational research is a popular buzzword in the biological sciences at the moment and granting agencies appear to believe that is what we should all be doing. It seems that the policy makers have discovered something that Moussa has been doing for much of his career: He has typified the ''from-the-laboratory-to-the-patient'' approach in the areas of monoamine oxidases and brain iron metabolism by developing them to their full extent in order to determine their physiological roles in the central nervous system, and then, by further pursuing them in the clinic. His continuing relationship with the pharmaceutical company Teva has been a key element in ensuring the success of these developments.

It is not the intention of this preface to reference Moussas' curriculum in detail. Indeed, it would be impossible in this short format to reference the seventy two pages of his CV and publications list. However, we would like to point to his incredible working capacity resulting in more than 450 original publications, some 220 full papers published in international symposia proceedings, the over 40 books and 96 invited articles, reviews, book chapters and commentaries – not to forget the 97 international patents awarded. As impressive as his scientific work is, and the list of awards, prizes and honours which he has received from around the world, perhaps most prestigious are the two Honorary Doctorate Degrees from the Universities in Budapest (1997) and Pisa (1998). Moussa is a member of 17 international scientific and professional associations and holds a current appointment on 19 editorial boards for international journals.

The list of graduate students and post-doctoral fellows is equally as impressive as that of the postdoctoral research associates that have worked with him. Together, they are creating ''Moussa's school of medicine''.

Finally, we would like to mention Moussa's talent of organizing and co-organizing international meetings and his extraordinary ability as invited plenary speaker.

Moussa is always fun to be with, spinning off ideas at a great rate and is seemingly able to carry on several detailed conversations simultaneously. Perhaps his inventive humour is best captured by naming the most successful amine oxidase workshop, which he organised in Haifa in 1996, ''MAO: the mother of all amine oxidases''. However, all of this is far from being meant as a valediction, and perhaps one day we will say that we ''shall not look upon his like again'' – and that will be true: Unless of course he invents an anti-death drug! But for now we can be glad that we have Moussa around and can be certain that he will continue to surprise and excite us with new developments and concepts.

''We are thankful, Moussa, for your friendship and open discussions. And we think that this collection of scientific work is a tribute which reflects your brilliant personality''.

Keith Tipton, Dublin
Hasan Parvez, Gif Sur Yvette
Peter Franz Riederer, Würzburg, March 2007

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Levodopa in the treatment of Parkinson's disease

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Summary Levodopa is the most efficacious drug to treat the symptoms of Parkinson's disease (PD) and is widely considered the "gold standard" by which to compare other therapies, including surgical therapy. Response to levodopa is one of the criteria for the clinical diagnosis of PD. A major limiting factor in levodopa therapy is the development of motor complications, namely dyskinesias and motor fluctuations. The ELLDOPA study was designed to determine if levodopa affected the progression of PD. This double-blind randomized study showed that the subjects treated with levodopa for 40 weeks had less severe parkinsonism than the placebo treated subjects even after a 2-week washout of medications, with the highest dose group showing the greatest benefit. Thus, levodopa may actually have neuroprotective value, but the result was not conclusive of slowing disease progression, because the same result could have arisen from a very long-lasting symptomatic benefit of levodopa.

Introduction

Parkinson's disease (PD) was first described in 1817 with the publication by James Parkinson of a book entitled "An Essay on the Shaking Palsy" (Parkinson, 1817). In it, he described six individuals with the clinical features that have come to be recognized as a disease entity. One of the people was followed in detail over a long period of time; the other five consisted of brief descriptions, including two whom he had met walking in the street, and another whom he had observed at a distance. Such distant observations without a medical examination demonstrates how readily distinguishable the conditions. The physical appearance of flexed posture, resting tremor, and shuffling gait are readily recognizable. Parkinson's opening description has the key essentials: "Involuntary tremulous motion, with lessened muscular power, in parts not in action and even when supported; with a propensity to bend the trunk forward, and to pass from a walking to a running pace: the senses and intellects being uninjured." In the small monograph, Parkinson provided a detailed description of the symptoms and also discussed the progressive worsening of the disorder, which he called "the shaking palsy" and its Latin term "paralysis agitans."

After the publication of Parkinson's book, the disease was widely accepted in the medical community. It took 70 years for the name of the disorder to be referred to as "Parkinson's disease," as recommended by the French neurologist Charcot who argued against the term "paralysis agitans" (see Goetz, 1987, for English translation). Charcot argued that there is no true paralysis, but rather the "lessened muscular power" is what is today called akinesia, hypokinesia or bradykinesia; all three terms often being used interchangeably. These terms represent a paucity of movement not due to weakness or paralysis. Similarly, Charcot emphasized that tremor need not be present in the disorder, so "agitans" and "shaking" are not appropriate as part of the name of the disorder.

Parkinson's disease (PD) vs. parkinsonism

The syndrome of parkinsonism must be understood before one can understand what is PD. Parkinsonism is defined by any combination of six specific, non-overlapping, motoric features, so-called cardinal features: tremor-at-rest, bradykinesia, rigidity, loss of postural reflexes, flexed posture and the "freezing" phenomenon (where the feet are transiently "glued" to the ground) (Fahn and Przedborski, 2005). Not all six of these cardinal features need be present, but at least two should be before the diagnosis of parkinsonism is made, with at least one of them being tremor-at-rest or bradykinesia. Parkinsonism is divided into four categories (Table 1). PD or primary parkinsonism will be the principal focus of this chapter; not only is it the one that is most commonly encountered by the general clinician, it is also the one in which levodopa is particularly

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Table 1. *Classification of the parkinsonian states*

I. Primary parkinsonism (Parkinson's disease)
Sporadic
Known genetic etiologies (see Table 2)
II. Secondary parkinsonism (environmental etiology)
A. Drugs
1. Dopamine receptor blockers (most commonly antipsychotic medications)
2. Dopamine storage depletors (reserpine)
B. Postencephalitic
C. Toxins – Mn, CO, MPTP, cyanide
D. Vascular
E. Brain tumors
F. Head trauma
G. Normal pressure hydrocephalus
III. Parkinsonism-Plus Syndromes
A. Progressive supranuclear palsy
B. Multiple system atrophy
C. Cortical-basal ganglionic degeneration
D. Parkinson-dementia-ALS complex of Guam
E. Progressive pallidal atrophy
F. Diffuse Lewy body disease (DLBD)
IV. Heredodegenerative disorders
A. Alzheimer disease
B. Wilson disease
C. Huntington disease
D. Frontotemporal dementia on chromosome 17q21
E. X-linked dystonia-parkinsonism (in Filipino men; known as lubag)

effective in ameliorating. Three of the most helpful clues that one is likely to be dealing with PD rather than another category of parkinsonism are 1) an asymmetrical onset of symptoms (PD often begins on one side of the body), 2) the presence of rest tremor (although rest tremor may be absent in patients with PD, it is almost always absent in Parkinson-plus syndromes), and 3) substantial clinical response to adequate levodopa therapy (usually, Parkinson-plus syndromes do not respond to levodopa therapy).

The great majority of cases of primary parkinsonism are sporadic, but in the last few years several gene mutations have been discovered to cause PD (Table 2). Whether genetic or idiopathic in etiology, the common denominator is that it is not caused by known insults to the brain (the main feature of secondary parkinsonism) and is not associated with other motoric neurologic features (the main feature of Parkinson-plus syndromes). The uncovering of genetic causes of primary parkinsonism has shed light on probable pathogenetic mechanisms that may be a factor in even the more common sporadic cases of PD.

Clinical description of Parkinson's disease

Although non-motor symptoms (e.g., constipation, aching shoulder, hypo-osmia, depression) may begin before the motor features of PD, these non-motor symptoms are too common in the general population to lead to a diagnosis of PD on their own. The motor symptoms of PD begin insidiously and gradually worsen. Symptoms, such as rest tremor, can be intermittent at the onset being present only in stressful situations. Symptoms tend to worsen on one side of the body before spreading to involve the other side. Rest tremor, because it is so obvious, is often the first symptom recognized by the patient. But the illness sometimes begins with bradykinesia, and in some patients, tremor may never develop. Bradykinesia manifests as slowness and small amplitude of movement, such as slower and smaller handwriting, decreased arm swing and leg stride when walking, decreased facial expression, and decreased amplitude of voice.

There is a steady worsening of symptoms over time, which, if untreated, leads to disability with severe immobility and falling. The early symptoms and signs of PD – rest tremor, bradykinesia and rigidity – are related to progressive loss of nigrostriatal dopamine and are usually correctable by treatment with levodopa and dopamine (DA) agonists. As PD progresses over time, symptoms that do not respond to levodopa develop, such as flexed posture, the freezing phenomenon and loss of postural reflexes appear; these are often referred to as non DA-related features of PD. Moreover, bradykinesia that responded to levodopa in the early stage of PD increases as the disease worsens and no longer fully responds to levodopa. It is particularly these intractable motoric symptoms that lead to the disability of increasing immobility and balance difficulties.

While it may be difficult to distinguish between PD and Parkinson-plus syndromes in the early stages of the illness, with disease progression over time, the clinical distinctions of the Parkinson-plus disorders become more apparent with the development of other neurological findings, such as cerebellar ataxia, loss of downward ocular movements, and autonomic dysfunction (e.g., postural hypotension, loss of bladder control, and impotence).

There are no practical diagnostic laboratory tests for PD, and the diagnosis rests on the clinical features or by excluding some of the other causes of parkinsonism. The research tool of fluorodopa positron emission tomography (PET) measures levodopa uptake into dopamine nerve terminals, and this shows a decline of about 5% per year of the striatal uptake. A similar result is seen using ligands for the dopamine transporter, either by PET or by single photon emission computed tomography (SPECT); these ligands also label the dopamine nerve terminals. All these neuroimaging techniques reveal decreased dopaminergic nerve terminals in the striatum in both PD and the Parkinson-plus syndromes, and do not distinguish between them. A