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IN MEMORIAM

In memoriam professor Philip Seeman (February 8, 1934-January 9, 2021)

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Professor Philip Seeman MD, PhD, DSc FRSC, Order of Canada, an ACNP Member Emeritus, was a towering icon of neuropsychiatric research. Inspired by his beloved wife and psychiatrist Dr. Mary V. Seeman, Philip became intrigued with schizophrenia pathophysiology. With the advent of effective antipsychotic drugs (e.g., haloperidol), he surmised that their targets could guide the path towards illuminating the pathology of schizophrenia. He acquired a radiolabeled form of haloperidol from its inventor, Dr. Paul Janssen. In 1974 he reported a seminal discovery that captivated the field of schizophrenia research: antipsychotic medications bound haloperidol-labeled sites at concentrations and with a rank order of potencies that correlated with the mean daily antipsychotic doses taken by patients with schizophrenia. He named the sites antipsychotic/dopamine receptors (later designated dopamine D2 receptors), based on the potency of dopamine. This achievement provided direct evidence for dopamine receptors, their relevance to antipsychotic drug activity and schizophrenia. It transformed dopamine receptor research by enabling in vitro screening for new antipsychotic drugs, by catalyzing the discovery of five dopamine receptor subtypes by cloning, and investigation of receptor subtype relevance to schizophrenia, Parkinson's disease, Huntington's Disease, addictive processes and endocrine disorders. Imaging of the D2 dopamine receptor in living human brain became feasible, and enabled discovery of the minimum D2 receptor occupancy (65%) for antipsychotic benefit, of the relevance of the D2 dopamine receptor to neuropsychiatric diseases, to addictive processes, to drug response, drug discovery, and measures of dopamine release. Dr. Seeman showed that many atypical antipsychotics rapidly dissociated from the D2 dopamine receptor, which he postulated could account for their diminished adverse neurological side effects; rapid offset times conceivably enabled periodic dopamine receptor activity and cycling to reduce maladaptations arising from uninterrupted receptor blockade. In later years, he found evidence for supersensitive D2 receptors in animal models of psychosis, which he postulated could explain the therapeutic benefit of D2 receptor blockade. In GWAS schizophrenia research, the D2 dopamine receptor gene has been ranked as highly associated with the disease. Current evidence indicates that polygenic mutations, brain injury, drug use, prenatal infection and malnutrition, social isolation and marginalization, are associated with symptoms of schizophrenia. Nonetheless, dopamine circuits are likely to constitute a final common route to many of the clinical symptoms, as they generally are alleviated by drugs that block dopamine D2 receptors.

Dr. Seeman cherished scientific research and practiced it compulsively and pragmatically. His 1980 review of dopamine receptors contained 1278 references, which he alone acquired in hard copy, cataloged by topic, read and underlined key sentences long before electronic media enabled keypress access to articles. He focused on core mechanisms and pathological unknowns, diagnostics and therapeutics. The impact of his research was recognized internationally. He was

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Our heartfelt sympathy extend to his wife, professor Mary V. Seeman and other family members.

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made an Officer of the Order of Canada and received numerous awards in Canada, the United States and in other nations. Dr. Seeman's towering research accomplishments live on in servers hosting ~800 articles and 56,000 citations (Google Scholar), and in a legacy of mentoring over 100 students, post-doctoral fellows and trainees. Philip Seeman's intangible traits - generosity, kindness, mentorship, friendship, equanimity, and humor - live on in the memories of those fortunate enough to have known him as a friend, a trainee, a colleague, an advisor, a collaborator.