

# Canadian College of Neuropsychopharmacology The First 25 Years

## PROLOGUE

Yvon D. Lapierre, M.D.

Chlorpromazine made its entry in North America in 1954 at the Verdun Protestant Hospital (now Douglas Hospital) in Montreal under the guidance of Dr. Heinz Lehmann. This landmark event changed the face of North American psychiatry and provided a significant impetus to the subsequent development of neuropharmacology and of psychopharmacology in Canada.

The activities of Canadian psychopharmacology at that time were mainly centered at McGill University and its affiliated hospitals in Montreal. The department of psychiatry and other disciplines interested in brain function gave the university a world-wide reputation as a mecca of learning of that era.

Training in psychopharmacology was limited as the discipline was in its infancy in great part because of the small number of therapeutic agents available. A listing of the therapeutic armamentarium of psychotropic agents would have barely covered one page. The list would have contained a preponderance of “old” drugs of the barbiturate variety that was in common use at the time. The discovery of the “major tranquilizer” chlorpromazine, however, was quickly followed by the discovery of the monoamine oxidase inhibitors, the tricyclic antidepressants and the benzodiazepines.

By the early 1960s, the pace of progress in neuropsychopharmacology accelerated by leaps and bounds. This level of activity led to the formation of groupings of basic and clinical scientists sharing common interests in many countries and to international collaborations. The Collegium Internationale Neuropsychopharmacologicum (CINP) initially brought the Europeans and Americans together in 1957. This was closely followed by the American College of Neuropsychopharmacology (ACNP) in 1961, the British Association of Psychopharmacology (BAP) in 1974 and the European College of Neuropsychopharmacology (ECNP) in 1986.

A number of other countries started forming groups with a common interest of pursuing the understanding of brain function. Initially, most of these societies were highly selective in their membership, and attendance at the scientific meetings was restricted. Sponsorship was a prerequisite for acceptance to membership. The original generation of Canadian researchers were often members of these societies and participated in their scientific activities.

By the mid 1960s, Canadian psychopharmacology activities remained centered mainly in Montreal at McGill University, the Université de Montréal, and a developing group at Université Laval, although the University of Toronto had by then also developed a significant presence in the field.

Communications between Canadian psychopharmacologists were person-to-person as there was no established forum to facilitate interactions. The collaborations between Canadians were on a personal level and were often not as frequent as those held with colleagues from other countries.

There were attempts made to establish formal structures, but these were often short-lived. One such attempt was spearheaded by Drs. Leon Tetreault and Jean-Marc Bordeleau of the Université de Montréal jointly with Drs. Heinz Lehmann and Thomas Ban of McGill University. This brought the researchers of these two universities and a few from Université Laval together as the Québec Psychopharmacological Research Association (QPRA).

The meetings of the Association were small and took place in the members' hospitals. There were no official publications arising from these meetings. Unfortunately, this turned out to be a short-lived effort and the organization did not survive the 1960s.

As the field of psychopharmacology progressed, a critical mass of clinical investigators and basic scientists focused on neuroscience and psychopharmacology was developing in Canada. It became apparent that collaborations between individuals and centers could reap benefits. The development of a Canadian identity could thus impact the future course of the discipline and its progress. Advances in knowledge and in technology were occurring rapidly, leading to more costly research and to more highly specialized interrelated disciplines. An illustrative example of that era was the burgeoning development of brain imaging techniques.

The pharmaceutical industry was also becoming more sophisticated in clinical research methodology in response to more stringent drug approval requirements. As available drugs were becoming more effective and statistical methodology more sophisticated, the era of single investigator protocols in clinical trials evaluating new therapeutics was closing and multicenter trials were becoming the norm for phase III studies. Consequently, the requirement of larger patient numbers and the time constraints of patient rights lead to the necessity of collaborations between centers. At that time, the Canadian research community was not fully ready for this type of collaboration and networking. On the other hand, there were several high caliber and internationally recognized investigators as well as smaller groups operating individually.

By the mid 1970s there were already a number of investigators who were expressing the need for increased communications and collaborations with other Canadian colleagues. The idea of a Canadian college lingered as an afterthought in a few of us and was brought up in individual conversations with senior colleagues who had also given it some consideration in the past, but the concept had not gone beyond that stage.

Dr. Yvon Lapierre had had some discussions seeking the advice of Dr. Heinz Lehmann, the godfather of Canadian psychopharmacology. The latter had been the moving force behind the QPRA. He still maintained a cautious attitude towards an undertaking of this type but encouraged it and promised to support it if it got going. Subsequently, further discussions were undertaken with colleagues including, among others, Joe McClure of Montreal and William Dewhurst in Edmonton who both supported the idea and expressed their interest in participating in the establishment of such an organization. This core group, plus a number of others, many of whom were already members of the CINP, was already a potential nucleus for a Canadian organization.

A pivotal event in the earliest phase was on October 18-19, 1976. Hoescht Pharmaceuticals hosted a small symposium at La Sapinière in Val-David, Quebec. This symposium was on Anxiety and Depression, and included a number of clinical investigators from across Canada and a few from out of the country. The two keynote speakers were Heinz Lehmann as the senior investigator and Yvon Lapierre as a relatively junior investigator. On the evening of October 18, during post-dinner conversation, Dr. Lapierre introduced the idea of a Canadian organization grouping those interested in psychopharmacology and its related disciplines. Participating in the discussion were Jean-Marie Albert, William Dewhurst, Maurice Dongier, Robert Elie, Paul Grof, Yvon Lapierre and Joe McClure. Dr. Joe Mendels was the only non-Canadian and a good person to present an impartial and constructively critical opinion on the concepts discussed.

A plan of action arose from the discussion. The participants realized that their enthusiasm might not be shared by those colleagues who were absent and particularly by the basic scientists

in the country. As is usual, the instigator of the discussion, Yvon Lapierre in this instance, was given the task of doing the initial reconnoitering of the Canadian scene. This was facilitated by already established working relationships. Dr. Radhey Singhal was then chairman of the department of pharmacology and Dr. Pavel Hrdina, professor in the department, was a well established and highly respected researcher in neuropsychopharmacology. They were immediately interested and agreed to seek the opinion of colleagues across the country on the feasibility of such an organization that would bring together Canadian basic scientists and clinical investigators. Should there be an adequate level of interest, it was decided that an informal gathering for further discussion and planning would be held the following spring. This was planned to take place during the annual meeting of the American Psychiatric Association in April, 1977.

An opinion survey of Canadian neuroscientists was conducted as a first step and then the views of clinician scientists and other investigators in psychopharmacology were elicited. The feedback from both of these groups was most encouraging. There was certainly felt to be a need for a Canadian association for those with an interest in brain function and its role in the causes, and the treatment, of mental illnesses.

The second step was to prepare a tentative preliminary format of such an association for discussion. Issues such as the name of the association, its level of academic standards, the extent of *rapprochement* with industry, the assurance of continued basic and clinical involvement etc, were amongst those points that had to be addressed.

*Authors' note* -To fully understand the environment of the day, views of the state of the art in basic science and in clinical psychopharmacology by individuals who were active at the time are inserted to give the reader a more complete appreciation of the respective eras.

## **NEUROPSYCHOPHARMACOLOGICAL RESEARCH IN CANADA IN THE 1970s**

Theodore L. Sourkes, Ph.D.

In the years just before the founding of the CCNP, the rigorous proof demanded by physiologists in an earlier era to establish the identity and authenticity of humoral neurotransmitters began to suffer erosion. The rules that were applicable to the vasomotor system and to the viscera were not applicable to the brain. Evidence for neurotransmitter function in that organ came from a variety of experimental studies involving diverse techniques. The break-through into the new mode came in the preceding decade through the collaborative, multidisciplinary work at McGill University and Université Laval in the laboratories of T. L. Sourkes and L. J. Poirier, respectively. This work established the first experimental model of Parkinson's disease: primates bearing specific unilateral cerebral lesions provided evidence for the existence of a neural connection between the substantia nigra and the striatum, functioning in the regulation of the movement of the limbs and employing dopamine as the neurotransmitter. By 1965-66 the role of dopamine as a neurotransmitter was assured. At the same time the central inhibitory action of gamma-aminobutyric acid (GABA) was being elucidated at the Montreal Neurological Institute in the laboratory of K.A.C. Elliott. In ensuing years similar status was gained for glutamic acid, glycine, and many other constituents of the central nervous system. The study of these neurotransmitters led to the blossoming of a new dimension in neuropsychopharmacology: the search for new drugs that act upon specific receptors, enhancing or limiting the physiological

responses to transmitters.

Fundamental research on neurotransmitters was at the same time associated with studies of the mode of action of the many new drugs that were being offered for the treatment of psychiatric disorders. As a result, Canadian research in these fields was well under way in the decade that saw the founding of the CCNP. The scope of this work is evident in the following capsule descriptions of some of the experimental laboratory and clinical research carried on in research centres across Canada:

Clinical trials of the therapeutic effects of neuroleptics in schizophrenia and other psychiatric conditions. The side effects of these drugs were of concern, especially tardive dyskinesia and parkinsonism.

Use of antidepressant drugs in affective disorders; studies of their biochemical and neurophysiological modes of action. Psychopharmacological properties of lithium salts. Tryptophan, as a source of cerebral serotonin in the treatment of mental depression; also in studies of behavioural states.

Investigation of primate models of Parkinson's disease. Experimental copper loading in search for a model of hepatolenticular degeneration (Wilson's disease).

Psychoneuroendocrinological factors in cognitive and affective states.

Role of neurotransmitters in various functions: dopamine in motivation and behaviour, and in the regulation of secretion from the anterior pituitary gland; acetylcholine in learning and memory; GABA and glycine in the actions of neuronal systems.

Psychopharmacology of apomorphine and amphetamine. Neurochemical mechanisms of action of opiates and other addictive drugs.

Neurological and hormonal regulation of the synthesis and release of amine neurotransmitters. Amine precursors (tryptophan, L-dopa) in neuropharmacological disorders.

## **CANADIAN CLINICAL PSYCHOPHARMACOLOGY IN THE 1970s**

Guy Chouinard, M.D. FRCP(C)

In the early 1970's, Montreal was a particularly active focus of investigations in psychopharmacology, with two major research centres: one at Douglas Hospital, at the time called the Verdun Protestant Hospital, and another at the St-Jean-de-Dieu Hospital, (now Louis-Hippolyte Lafontaine). Hôpital St-Michel Archange (now CH Robert-Giffard) also had a psychopharmacology research center.

At Douglas Hospital, psychopharmacology was directed by Dr. Heinz E. Lehmann and Dr. Thomas Ban. This institution attracted students in psychopharmacology from around the world to train in this clinical discipline. Among them, one Fellow at Douglas Hospital was Dr. B Saxena, who went on to direct psychopharmacology at the Hamilton Psychiatric Hospital and J.V. Ananth who later moved to UCLA in Los Angeles. At that time, Dr. T. Ban was writing his textbook on psychopharmacology and, later on, Dr. H.E. Lehmann co-chaired the Le Dain Royal Commission on the use of marijuana and other hallucinogenic drugs.

In the early 1970's, residents in psychiatry were attracted to Douglas Hospital to do their training, and one of them was Dr. Guy Chouinard, who did his early studies on neuroleptics in that setting. The French-language counterpart was lead by the renowned methodologist, Dr. Léon Tétrault, with Dr. Jean-Marc Bordeleau, a clinical investigator. They jointly headed the research center at St-Jean-de-Dieu Hospital. One of their students and eventual collaborators was Dr.

Gilbert Pinard, who later became the chairman of psychiatry at the University of Sherbrooke and chairman of psychiatry at McGill. Dr. Rejean Gauthier and Dr Marc-Andre Gagnon also assisted with the research on psychostimulants. Dr. L. Tétreault had students pursuing master's degrees in pharmacology, one of whom was Dr. G. Chouinard, who worked on the methyl dopa-chlorpromazine interaction. One previous student of Dr. L. Tétreault's was Yvon Denis Lapierre, who later established a research unit in psychopharmacology first in Pierre Janet Hospital in Hull and then at the University of Ottawa. Led by Dr. Lapierre, the Ottawa centre became one of the most active in clinical research in psychopharmacology. In 1978 Dr. Lapierre led a group of Canadian psychopharmacologists to found the CCNP.

In 1972, Lawrence Annable came from England to join the team at Louis-Hippolyte Lafontaine and started working with Dr. G. Chouinard in 1973 on the amitriptyline-perphenazine interaction in schizophrenic patients. Then Professor Annable moved to McGill University and the Allan Memorial Institute, where Dr. M. Dongier was the newly appointed director. It was with the arrival of Lawrence Annable and in concert with Dr. G. Chouinard that the Allan Memorial Clinical Psychopharmacology group was established. Both researchers joined Dr. Thomas Kolivakis, who was already doing psychopharmacology research. Annable's research in clinical psychopharmacology, in particular in the area of abnormal movement disorders, subsequently led to the development of the Extra-pyramidal Symptom Rating Scale (ESRS) by Dr. G. Chouinard. During the same period, Dr. André Villeneuve and his group, which included Drs. Karolina and Andrzej Jus, were also working on abnormal movements. They were the first to describe the Rabbit Syndrome, a tardive lip tremor associated with neuroleptics.

The Allan Memorial Psychopharmacology Research Unit started expanding and work on clozapine was initiated. One of the first studies of clozapine was also done at the same time in Ottawa by Dr. Y.D. Lapierre. At both Hôpital Louis-Hippolyte Lafontaine and the Allan Memorial Institute, several clinical trials were undertaken in the areas of both affective disorders and schizophrenia and were supported by the Canadian Medical Research Council. These clinical trials included work on tryptophan in psychiatric disorders such as depression and mania. Clinical research was also done with Dr. M. Dongier on post-operative negative variation in schizophrenia, benserazide in schizophrenia, electro-cardiographic abnormalities induced by anti-psychotics with the Institut de Cardiologie de Montreal, rubidium in schizophrenia, penfluridol in schizophrenia, and adverse effects on anti-parkinsonian medication in schizophrenia. Other work focused on depot injectable antipsychotics, such as pipothiazine palmitate and fluphenazine decanoate as outpatient treatment of schizophrenia was associated with a high incidence of non-compliance.

At the end of the 1970's, Dr. Barry Jones joined the Allan Memorial Institute in Clinical Psychopharmacology to train. He was later involved in several research projects, among which was the development of the concept of supersensitivity psychosis. Other clinical research at the time included the genetics of manic-depressive illness and a theory of schizophrenia regarding dopamine deficiency. Also initiated were epidemiological studies of Drug Induced Movement Disorders at both Hôpital Louis-Hippolyte Lafontaine and the Allan Memorial Institute.

The Allan Memorial Psychopharmacology Research Unit started a collaboration with Dr. Simon Young and Dr. Ted Sourkes, and tryptophan clinical studies were initiated with nicotinamide in affective disorders. There were also investigations of the interaction between lithium and tryptophan in both mania and depression. Dr. T. Sourkes and Dr. S. Young were international leaders in basic neurosciences at the Allan Memorial Institute.

A third center was also established at the Montreal General Hospital and was headed by

Dr. Joe McClure. This centre focused on the treatment of depression and biogenic amines.

The Clinical Psychopharmacology Research Unit at the Allan Memorial Institute and Hôpital Louis-Hippolyte Lafontaine became an important research unit along with Dr. Y.D. Lapierre's research unit and Dr. N.P.V. Nair's research unit at Douglas Hospital. Several Canadian multi-centre antidepressant trials on fluoxetine, sertraline, and bupropion were initiated at the end of the 1970s. New concepts in pharmacotherapy with benzodiazepines were also developed following the discovery of the therapeutic effects of clonazepam in psychiatric disorders, first in mania, then in panic disorders, and the discovery of alprazolam as the first drug officially approved for panic disorders.

At the Allan Memorial Institute, Dr. Jacques Bradwejn also trained and worked on the antidepressant effects of tomoxetine, which was later developed for other indications. Dr. A.M. Ghadirian, who came from Ottawa, was also at the Allan Memorial Institute and started investigations of sexual dysfunction and plasma prolactin levels in neuroleptic-treated schizophrenic patients. Dr. Claude de Montigny joined Dr. G. Chouinard at Hôpital Louis-Hippolyte Lafontaine for one year of training in clinical psychopharmacology, during which time studies of loxapine, deanol and anticholinergic effects on tardive dyskinesia were carried out. He later did his studies on lithium potentiation of antidepressants at Hôpital Louis-Hippolyte Lafontaine and then moved to McGill to establish a neuropharmacology laboratory. Dr. Roberto Collu, who later became president of the Medical Research Council, was also active in neuroendocrinology and participated in the research work at Hôpital Louis-Hippolyte Lafontaine on prolactin. He investigated the role of prolactin elevation induced by antipsychotics in the assessment of the anti-psychotic effects with the Hôpital Louis-Hippolyte Lafontaine.

In conclusion, Canadian clinical psychopharmacology in the 1970's was much involved in the evaluation of the side effects associated with neuroleptics and the development of depot injectable antipsychotics, and at the end of this period, several major clinical studies with the second generation of antidepressants were initiated.

#### *Planning Meeting-Toronto-April 1977*

On a bright April morning, Drs. Lapierre, Singhal and Hrdina took an early Air Canada flight from Ottawa to Toronto. Arrangements had been made by Dr. McClure for a meeting room at the Royal York Hotel which would accommodate the hoped-for 40 people who had expressed an interest in attending. Those were anxious moments indeed. The threesome shared an apprehensive expectation, fully realizing that the outcome of this meeting would have a significant impact on the future of the planned organization. There was an analogy drawn to Alexandre Dumas's "Three Musketeers", without the youngest, d'Artagnan. There had been some reassurance from Joe McClure, who was on site attending the American Psychiatric Association meeting, that the room would not be empty.

The meeting had been scheduled during the lunch hour and some sandwiches and coffee were provided. The costs were covered by a pharmaceutical company as there were no other funds available. The room quickly filled with 40 attendees showing up, to the satisfaction and relief of the organizers (see list of attendees below). It was most reassuring to see the faces of veterans such as Drs Heinz Lehmann, Joel Elkes and Harvey Stancer who represented the first generation of Canadian psychopharmacologists. It was comforting to hear the reminiscences of Drs Lehmann and Elkes on their experiences in the establishment of the ACNP many years previously.

Yvon Lapierre chaired the meeting and Pavel Hrdina acted as secretary. The first issue

discussed was the appropriateness and even the necessity for a Canadian association when already established organizations such as the ACNP and the CINP in other countries were available as conduits for Canadians who wished to be involved with other colleagues. This debate was necessary for a “buy-in” and resulted in a consensus and a commonality of purpose that proved to be crucial subsequently. The importance of having a Canadian group was recognized and agreed upon by an overwhelming majority of those present.

The second issue was the type of organization that should be established. The British had chosen an “association” whereas the Americans and Europeans had opted for a “college”. The great majority of the participants were in favor of the term “College” as preferable for home consumption and for international image. It would also be more congruent with the objectives of excellence which we all strived for.

The issue of the degree of inclusiveness or exclusiveness was discussed and input was received. The complexities were such that it was referred to the steering group for formulation of guidelines for membership to be approved by the membership subsequently. The initial input suggested that any professional who was actively engaged in research and had meritoriously published in the field of neuropsychopharmacology should be eligible as a candidate for membership.

It was also agreed that the scientific meetings should be held annually. A steering committee was established from the participants present. The chairman for the group was Yvon Lapierre of Ottawa. The other members appointed were:

William Brown-Vancouver  
William Dewhurst- Edmonton  
Paul Grof- Hamilton  
Pavel Hrdina- Ottawa  
Ed Kingstone- Toronto  
D. Joe McClure- Montreal  
David Paton- Edmonton  
Radhey Singhal- Ottawa  
André Villeneuve- Quebec

Three *ad hoc* committees were formed to initiate the organizational process. These were:

- 1-Constitution and Membership committee
- 2-Finance and Liaison committee
- 3-Scientific and Program committee

The Constitutional Committee was to:

- 1-prepare a constitution in which the objectives and scope of the College would be defined
- 2-propose the bylaws for the organization to lead it to becoming a legal entity
- 3-propose guidelines for membership eligibility.

The initial suggestions were for four types of membership: Honorary, Regular (active), Supporting and Foreign.

The Finance and Liaison Committee was mandated to propose guidelines for the establishment of administrative, professional, academic and scientific relationships with other professional,

academic, governmental and industrial organizations. The steering group was also requested to arrange for the financing of the association and to make arrangements for the first scientific meeting. The role of treasurer was assigned to Joe McClure.

The Scientific and Program Committee was mandated to select the location and timing of the first scientific meeting, to prepare the scientific program and to make the local arrangements of the first meeting. The committee was also mandated to arrange for publication of the scientific presentations of the founding meeting.

Dr Joe McClure headed the local organizing committee for the first scientific meeting which was to be held the following spring at St. Mary's Hospital, an affiliate of McGill University in Montreal. The responsibilities for the scientific program of the first meeting were assigned to Drs. Pavel Hrdina and Radhey Singhal.

The initial and preliminary objectives of the organization were then envisaged as:

1- a forum for clinical and basic science researchers to discuss and exchange ideas and experiences in neuropsychopharmacology and to promote the development of this science nationally and internationally.

2- a liaison body to educational institutions, public, industry and government organizations as well as other related scientific bodies in order to promote quality of research and treatment in this field.

The mandate given to the steering committee was to draft a constitution and to establish legal and fiscal structures for the College.

During the intervening months from the initial planning to the first scientific meeting, Yvon Lapierre drafted the constitution with the collaboration of Radhey Singhal and Pavel Hrdina. The initial draft was a blended adaptation of the constitutions of the CINP and of the ACNP, with the adjustments to the Canadian scene. Mr. Robert Baldwin of the firm Houlahan and Baldwin in Ottawa assisted. This law firm had previous experience in the incorporation of non-profit organizations. Mr. Baldwin was consulted on the legal issues of incorporation and on the most appropriate tax and fiscal status for the College. There were regular communications with other members of the steering group for broader based input into these basic but also crucial documents.

Finally, the Letters Patent of Incorporation were confirmed by the Minister of Consumer and Corporate Affairs of Canada on May 22, 1979 and recorded 28<sup>th</sup> September, 1979. The first directors of the Corporation were Y.D. Lapierre, W. G. Dewhurst, R.L. Singhal, P.D. Hrdina, J. McClure, W. Brown, W. Davidson, G.M. McKenzie, A. Villeneuve and E.C. Vos.

Participants of the organizational meeting of the CCNP  
Royal York Hotel, Toronto- May 2, 1977

|               |   |
|---------------|---|
| Amin M.       | McGill University (Psychiatry)              |
| Brown W.M.T.  | University of British Columbia (Psychiatry) |
| Capek R.      | McGill University (Pharmacology)            |
| Chouinard G.  | McGill University & Université de Montréal  |
| Dewhurst W.G. | University of Alberta (Psychiatry)          |
| Elkes J.      | McMaster University (Psychiatry)            |

|                   |   |
|-------------------|---|
| Grof P.           | McMaster University (Psychiatry)                |
| Hrdina P.D.       | Ottawa University (Pharmacology)                |
| Jhamandas K.      | Queens University (Pharmacology)                |
| Kingstone E.      | University of Toronto (Psychiatry)              |
| Lapierre Y.D.     | Ottawa University (Psychiatry/Pharmacology)     |
| Laverty G.        | Queens University (Psychiatry)                  |
| Lehmann H.E.      | McGill University (Psychiatry)                  |
| Leichner P.P.     | Queens University (Psychiatry)                  |
| Letemandia Felix  | Queens University (Psychiatry)                  |
| MacCrimmon D.J.   | McMaster University (Psychiatry)                |
| McClure D.J.      | McGill University (Psychiatry)                  |
| McKenzie G.M.     | Dalhousie University (Pharmacology)             |
| Nair N.P.V.       | McGill University (Psychiatry)                  |
| Pecknold J.C.     | McGill University (Psychiatry)                  |
| Pinsky C.         | University of Manitoba (Pharmacology)           |
| Radouco-Thomas C. | Université Laval (Pharmacology)                 |
| Radouco-Thomas S. | Université Laval (Pharmacology)                 |
| Saxena B.M.       | McMaster University (Psychiatry)                |
| Sen A.K.          | University of Toronto (Pharmacology)            |
| Singh A.N.        | McMaster University (Psychiatry)                |
| Singhal R.        | Ottawa University (Pharmacology)                |
| Stancer H.C.      | University of Toronto (Psychiatry)              |
| Stretch R.        | Ottawa University (Pharmacology & Psychology)   |
| Villeneuve A.     | Université Laval (Psychiatry)                   |
| Warsh J.J.        | University of Toronto (Psychiatry/Neuroscience) |

#### *Founding Scientific Meeting*

The initial scientific meeting was pivotal in determining the future of the CCNP. Not only were the structural foundations of the organization to be established, but most importantly, the “raison d’être” of the CCNP was to be demonstrated by the quantity and the quality of the scientific papers that would be presented.

The Steering Committee met on 19 April 1978. The business meeting to be held during the plenary sessions the following day required detailed preparation. The Steering Committee, appointed the previous April, had not yet had a formal face-to-face meeting where the interactions of the various viewpoints could be debated.

A block of rooms had been reserved at the old Windsor hotel in Montreal which included a suite to accommodate the meeting of the Steering Committee. It was crucial that a consensus be reached on the essential issues up for discussion the next day. The draft constitutional issues and *modus operandi* for the next few years had to be established. There were many additional suggestions made that addressed the needs of the future membership across the country.

A few issues required longer discussions and compromise. An example of this was the role of the pharmaceutical industry in the College. The delicate balance between the financial, professional and ethical considerations needed frank discussion to eventually strike the appropriate balance of these multiple interests within the organization.

The appropriate recognition of the early contributors in the multiple and diverse aspects of Canadian neuropsychopharmacology would contribute to the historical seriousness of the

College. The thorny and sensitive issues of membership required a consensus of the group before the open discussion in the general meeting. It was decided that we would have a category of “Honorary Fellow” and the choice of candidates for this honour was discussed at length. Those who were felt to merit this recognition at that time were R.A. Cleghorn, J. Elkes, H.E. Lehmann, J. Quastel and G.J. Sarwer-Foner.

At the first plenary business meeting the next day, there was a total of 44 participants (appendix IV). The issues were again discussed in detail with new input and then voted on item by item. The aims were clearly stated and agreed to by those present. They were to be Article 2 of the constitution:

1-to provide a forum for clinical and basic science researchers to discuss and exchange ideas and experiences in neuropsychopharmacology and to promote the development of this science nationally and internationally.

2-to be a liaison body to educational institutions, public, industry and government organizations as well as other related scientific bodies to thus promote the quality of research and treatment in this field.

Elections were held and the first slate of officers was chosen as:

|                  |   |
|------------------|---|
| President-       | Y. D. Lapierre  |
| Vice-presidents- | W.G. Dewhurst (clinical)<br>R. L. Singhal (basic science)           |
| Secretary-       | P. D. Hrdina  |
| Treasurer-       | D. J. McClure   |
| Councillors-     | W. Brown<br>W. Davidson<br>G.M. McKenzie<br>A. Villeneuve<br>E. Vos |

The working committees were established with R. Capek, P. Grof, G. Pinard and B. Saxena as chairmen. There were provisions for amendments to be initiated from the Council as well as from the membership. It was expected that changes would be required in the ensuing years as the College would have to adapt to changing times.

The scientific program was a remarkable success. The networking that had been hoped for did take place and potential working relationships were nurtured. The scientific presentations were of a high caliber, with presentations from some of the leading Canadian scientists. There were two leading symposia; one on “Schizophrenia: Aetiology and Pharmacology” and the other on “Endorphins”, a high profile topic at the time. In addition, 14 free communications from a number of academic centers were illustrative of the clinical and basic science activities across the country.

Networking through loosely structured social activities is an essential component of a nascent organization. The talent of Dr. McClure was put to the test and quite successfully so. There were a number of planned breaks as opportunities for strengthening collegiality. A memorable lunch sponsored by St. Mary’s Hospital was held at Paesano’s, a charming Italian restaurant within walking distance of the hospital.

A record of the scientific presentations was of historical and psychological importance for those who had committed to the College. The 215 page binder of “The Proceedings of the

Founding Meeting” was published to the membership with the support of Pfizer Pharmaceuticals.

List of Participants of the Founding Business Meeting  
St Mary’s Hospital, McGill University April 20, 1978

|                          |                               |
|--------------------------|-------------------------------|
| Amara I.B.               | Queens University             |
| Ananth J.                | McGill University             |
| Bourgouin M.             | Sandoz Pharmaceuticals        |
| Brands B.                | University of Western Ontario |
| Brown G.M.               | McMaster University           |
| Chiz J.F.                | Schering Corporation          |
| Dewhurst W.G.            | University of Alberta         |
| Dressler M.C.            | Hoffman-LaRoche               |
| Elie R.                  | Université de Montreal        |
| Forgiel W.J.             | McNeil Laboratories           |
| Gee H.W.                 | E.R. Squibb & Sons Ltd.       |
| Germain M.               | Ciba-Geigy Pharmaceuticals    |
| Giering J.E.             | Pennwalt Pharmaceuticals      |
| Grof P.                  | McMaster University           |
| Hoffman C.H.             | Upjohn Pharmaceuticals        |
| Hosein E.A.              | McGill University             |
| Hrdina P.D.              | Ottawa University             |
| Huynh T.                 | A.H. Robins Ltd.              |
| Jeffery H.               | Pfizer                        |
| Jhamandas K.             | Queens University             |
| Kolivakis T.             | McGill University             |
| Lapierre Y.D.            | Ottawa University             |
| Leonard W.E.             | Hoffman-LaRoche               |
| Marshall A.M.            | University of Western Ontario |
| Mazurkiewicz-Kwilecki I. | Ottawa University             |
| McKenzie G.M.            | Dalhousie University          |
| McClure D.J.             | McGill University             |
| Merali Z.                | Ottawa University             |
| Neuman R.S.              | Memorial University           |
| Pearce K.I.              | University of Calgary         |
| Pinard G.D.              | Université de Sherbrooke      |
| Pivik R.T.               | Ottawa University             |
| Rochefort J.G.           | Abbott Laboratories           |
| Sarrazin R.              | Poulenc                       |
| Saxena B.                | McMaster University           |
| Singhal R.L.             | Ottawa University             |
| Sourkes T.L.             | McGill University             |
| Stancer H.C.             | University of Toronto         |
| Tacreiter A.W.           | ICI Americas                  |
| Tubb M.C.                | Fisons Corporation            |

|               |                       |
|---------------|-----------------------|
| Villeneuve A. | Université Laval      |
| Warsh J.J.    | University of Toronto |
| Vos E.C.      | SmithKline & French   |
| Young S.N.    | McGill University     |
| Zarowny D.    | Hoffman-LaRoche       |

#### Delegates in training

Berliss Herman  
Delva Nicholas  
Fang Ta-Yun  
Gagnier Jean-Pierre  
Gauthier Serge  
Hinson Joseph  
Jones Barry  
Kokkinidis Larry  
Monpremier Pierre  
Oyewumi Kola  
Ramirez-Gonzalez Dolores

Once the proposed constitution was approved, the steering committee put forth a list for approval as founding fellows. To the initial list at the meeting were added a few who had not confirmed their intent earlier. These are listed as follows:

#### List of Approved Founding Fellows as of 2 February, 1979

Amin M.  
Ananth J.  
Boulton A.A.  
Brown G.M.  
Brown W.T.  
Capek R.  
Chouinard G.  
Davidson W.J.  
Dewhurst W.G.  
Dongier M.  
Grof P.  
Hrdina P.D.  
Jhamandas K.  
Kingstone E.  
Lapierre Y.D.  
Lavery G.  
Leichner P.P.  
Letemendia F.  
MacCrimmon D.J.  
McClure D.J.  
McKenzie G.M.

Nair N.P.V.  
Pecknold J.C.  
Pinsky C.  
Pivik R.T.  
Radouco-Thomas C.  
Radouco-Thomas S.  
Saxena B.  
Sen A.K.  
Singh A.N.  
Singhal R.L.  
Sourkes T.  
Stancer H.C.  
Stretch R.  
Villeneuve A.  
Vos E.C.  
Warsh J.J.

The founding of the CCNP was announced to the world of neuropsychopharmacology through a variety of professional journals and through the CINP, ACNP the Royal College of Physicians and Surgeons of Canada, the pharmaceutical industry, and European societies.

#### *Second Annual Meeting- Hamilton*

The second scientific meeting was held at McMaster University in Hamilton in April, 1979. The Council meeting of 25<sup>th</sup> April, 1979 addressed the issue of membership which, after one year of experience, was becoming simpler to deal with for the organizers. Continuity and precedent-setting for the ensuing years was of concern to the group. For stability and maturity to develop, it was necessary for the structures to promote the recognition of our pioneers in the field and that the contributors of today be recognized in the future. The discussions focused on how to initiate the process to arrive at these objectives with the intent that these processes remain dynamic and readily adaptable to change in the future.

Publication of the proceedings was at the forefront of the discussions at this meeting. The most appropriate venue for credibility and the greatest degree of dissemination of the scientific activities of the members was being explored through commercial and academic venues but we were unable to arrive at a satisfactory solution at that time. As an interim solution, the publication of this Hamilton meeting was in book form entitled "Recent Advances in Canadian Neuropsychopharmacology" edited by P. Grof and B. Saxena and published by Karger.

The financial planning was reviewed and a "nest-egg" for future developments was started with an initial first year surplus of \$3,678.36. This was in great part the result of the astute management of Bishan Saxena.

The Scientific Program Committee was under the chairmanship of Radan Capek. These being formative years for the organization, the Scientific Program Committee and the Local Organizing Committee interacted during the preparatory months to establish some of the groundwork on procedures which would serve as the base for organizing future meetings. These included having plenary lectures from distinguished researchers, combinations of oral and poster presentations and opening the door to members of the College to allow all the members the opportunity of presenting their work.

The second meeting was a success thanks to the organizational skills of Paul Grof and Bishan Saxena. An innovation at this meeting was a session on “The Teaching of Psychopharmacology.” This was included as a first step in addressing the educational objectives of the CCNP.

#### *Third Annual Meeting-Edmonton*

The third meeting of the CCNP was held at the University of Alberta in Edmonton 3 May 11-13, 1980, organized by William Dewhurst and Glen Baker. This being the first meeting in Western Canada, it served as a concrete expression of the national objectives of the college. By then, the CCNP was evolving into a truly national organization. The legalities were completed and were official. It was now a federally incorporated non-profit organization with the tax status of such. The financial base was becoming more firm as the first long-term deposit of \$5,000 to establish a financial reserve was approved by council. The proceedings of the previous meeting held in Hamilton were in process of being published by Karger, an international publisher. This book was entitled “Recent Advances in Canadian Neuropsychopharmacology”. The proceedings of the Edmonton meeting were published in the *Canadian Journal of Neurological Sciences*.

The membership committee was becoming more selective in its recommendations for new fellows. The meetings for the next two years were in the planning process and reflected the developing membership and interest of all areas of the country. Finally, the term of the first roster of elected executives ended and a new executive under the presidency of Dr Radhey Singhal was installed for a two-year term.

Along with this came new initiatives which added to the character of the organization. The most significant of these was the initial planning for CCNP awards for outstanding contributions to Canadian Neuropsychopharmacology. A committee (Sourkes, Lapierre and McClure) was established to initiate the process.

#### *Fourth Annual Meeting-Toronto*

Preparations for the fourth annual meeting were under the able direction of Drs. J.J. Warsh and A.G. Awad. The meeting took place April 23-25, 1981 in the facilities of the Clarke Institute of Psychiatry and The Addictions Research Foundation. By then, the functioning of the committees and clarification of responsibilities were becoming clearer and terms of reference continued being developed as the roles of committees jelled.

The guidelines of the Heinz Lehmann Award were developed and the initial sponsor, Hoffman-LaRoche, undertook a long term commitment of support. From its conception, this award was meant to be the flagship of the CCNP in the recognition of contributions to psychopharmacology in Canada. Mr. M.C. Dressler, senior vice-president of Hoffmann-LaRoche, was an early enthusiastic supporter of Canadian medical research. He gave unwavering support on behalf of his company to the establishment of the award and Hoffmann-LaRoche undertook a five-year commitment to provide the monetary support of \$3,000 annually and to have a senior member of the firm to make the presentation. In fact, for a number of years, the president made the presentation on behalf of the College, starting off with Mr. Charles Barrelet in 1982 at the meeting held in Quebec City. Subsequently, other Hoffman-LaRoche CEOs followed in the tradition, including Aldo Baumgartner and Don Brown.

Publication of the proceedings was still an issue difficult to resolve. Dr C. Radouco-Thomas, the then editor-in-chief of *Progress in Neuropsychopharmacology* volunteered that journal to help in the publication of the papers of the meeting.

The first sign of international recognition of the College appeared with an offer from the British Association for Psychopharmacology (BAP) for membership reciprocity including presentation of papers at their meetings and the waiving of registration fees. Reciprocal courtesies from the CCNP were immediately extended.

*CCNP Meetings, 1980s, '90s & 2000s*

At the sixth meeting, which was held in Saskatoon in 1983, relationships with the ACNP started developing with the announcement that three CCNP members would be invited to their annual meeting which had hitherto been strictly limited to their members and their guests. In a similar vein of international relations, initial contacts were established with the BAP which would result in collaborative undertakings within a few years.

As would normally be expected, the constitution and by-laws were reviewed and adjusted to the times. They were then written in the two official languages of the country. By then, the membership had increased to 122 fellows, 6 affiliate members and 28 institutions as affiliate members.

After having taken place in a number of other Canadian sites including Quebec, London, Halifax, the College convened in Ottawa for its 10<sup>th</sup> anniversary meeting. Towards the end of the 1980's, joint meetings with other national societies started occurring. The first of these was in Cambridge, England with the BAP, July 23-26, 1989. Reciprocity was rendered four years later when the BAP came to Montreal for the CCNP's 16<sup>th</sup> meeting followed by a second encounter in Cambridge for another joint meeting in 1993.

The Association Française de Psychiatrie Biologique was invited to the 17<sup>th</sup> meeting held in Quebec City in 1994 and reciprocated for the 2000 meeting (23<sup>rd</sup>) held in Marakesh. The 1995 meeting was jointly held with the Japanese Society of NeuroPsychopharmacology (JSNP) in Vancouver. The 24<sup>th</sup> meeting held in Banff was even more international with the participation of the CCNP, BAP and JSNP. Finally, the 25<sup>th</sup> meeting returned to Ottawa in 2002, thus bringing about the completion of the first quarter century.

## **PSYCHOPHARMACOLOGY RESEARCH IN THE 1980s: AN ERA OF GREAT OPTIMISM**

A.G. Awad, M.D., Ph.D.

To review psychopharmacology research in the 1980s is to write about the accomplishments of the CCNP in its first full decade, following its creation in 1978. The decade of the 1980s truly represents an era of great optimism in psychopharmacology research in Canada. Basic and clinical research flourished in Canada through the development of specialized psychopharmacology programs in most of the major universities from East to West. In Dalhousie University, H. Robertson established his research in behaviour and *c-fos* expression of the dopamine receptors, particularly in Parkinson's disease. In the University of Ottawa, Y. Lapierre developed a strong Psychopharmacology Program, with extensive clinical trials as its central piece. P. Hrdina continued his research in pharmacokinetics and serotonergic markers of depression. In McGill University, which had led the early psychopharmacology development, not only in Canada, but across North America, C. de Montigny and his group explored the mechanisms of action of antidepressants and lithium. T. Ban advanced Neuropsychopharmacology research by his emphasis on methods to quantify psychopathology. G. Chouinard, V. Nair, and J. Ananth advanced neuropsychopharmacological research by

creating strong clinical trials programs of psychotropic medications. In Laval University, A. Villeneuve headed a research program in affective disorders and neuroendocrine aspects of psychiatric disorders. In McMaster University, E. Kingstone and J. Cleghorn advanced psychopharmacology research in schizophrenia and mood disorders, and also created a major presence in the PET imaging facilities there. In the University of Toronto, H. Stancer established a strong program in mood disorders research. O. Hornykiewicz continued his pioneering work in levodopa and Parkinsonism. A. Boulton developed a strong program in biological markers in neuropsychiatric disorders in the University of Saskatchewan. W. Dewhurst, R. Coutts and G. Baker developed a successful neurochemical research program in the University of Alberta in Edmonton. In the University of British Columbia, C. Fibiger and A. Phillips established a strong program in neurochemical substrates of motivation and emotion. These are a just few examples and not intended to be a full survey of researchers or research activities in these centres, but to demonstrate the major growth and enthusiasm about neuropsychopharmacology research. Not only did these centres advance the research enterprise but also served as training magnets for a large group of young researchers, many of whom are now the leaders in the field.

The decade of the 1980s is significant in being a decade of transition between the old and the new antidepressants and antipsychotics. The clinical trials of what would have been the first selective serotonin inhibitor antidepressant, Zimeldine, were undertaken in Canada, leading to its approval. Unfortunately, Zimeldine was withdrawn shortly after, due to unexpected serious side effects that were not predicted in the clinical trials. Clinical trials with Prozac also started at full-speed, upon the heel of Zimeldine being withdrawn from the market. Clinical trials with Remoxipride and Risperidone continued in earnest, leading to their approval in the early 1990s. Unfortunately, Remoxipride had to be withdrawn, as the result of unpredicted serious side effects.

Ushering in the era of new antidepressants and antipsychotics brought in the recognition of the relatively high cost of these medications. As in any transition stage, the value of the new benefits compared to the high cost of acquisition inevitably raised questions about cost-effectiveness and cost-utility. This issue was anticipated in the 1980s and led to the early development of Pharmacoeconomic studies, particularly “Cost-Utility Analysis” as well as a shift in expectations of outcomes of drug therapy. The emphasis had shifted not only from improvement in symptoms but also to improved outcomes such as quality of life, compliance and improved functionality. It was not long before interest in such issues spread from the work of Awad and Voruganti in Toronto to virtually all the major centres to become an important component of the clinical trials of psychotropic medications.

One of the reasons for the great optimism in the 1980s was related to a burst of research funding by the federal government, in creating centres of excellence, with psychopharmacology as a major component in all networks established in depression, schizophrenia and dementia. As usual, the government research funding was not maintained after the initial phase of development, which led to the break-up of some networks. However, the depression network seems to have survived and led in a later decade to the creation of CANMAT (Canadian Network for Mood and Anxiety Treatment). CANMAT has been successful not only in coordinating research in mood disorders, but also in serving an important role in educating professionals and the public about the treatment of mood and anxiety disorders.

Returning to the CCNP and how all that relates to its progress, the College not only fostered and showcased the research development but also served as a home-base for researchers, both clinical and basic scientists. The decade of the 1980s followed a very successful first

meeting of CCNP in Western Canada. In 1979, Glen Baker and his colleagues, by organizing a strong CCNP Meeting in Edmonton, brought Western Canada in, joining Eastern Canada in the strong development of the College.

One of the major problems in recollecting history is the inherent personal bias in presenting these historical notes. Henceforth, I prefer to call my historical notes personal reflections. I had the distinct pleasure and privilege to serve the CCNP as its 10<sup>th</sup> President during 1994-1996, an era that witnessed the establishment of closer links between CCNP and the BAP, the ECNP, the ACNP, the JSNP as well as the CINP. I am optimistic that the next twenty-five years will witness major growth of the CCNP, as a reflection of the continued and enhanced neuropsychopharmacology research in Canada

## **CANADIAN BASIC SCIENCE ACTIVITIES IN NEUROPSYCHOPHARMACOLOGY IN THE 1980s**

Glen B. Baker, Ph.D.

Although many advances in neuropsychopharmacology were made in the 1980s, perhaps the most notable strides were made in studies on the mechanisms of action of antidepressants, antipsychotics and the benzodiazepines. Because of these studies, much was learned about receptors and transduction mechanisms involving the biogenic amines noradrenaline (NA), 5-hydroxytryptamine (5-HT, serotonin) and dopamine (DA) and amino acids, particularly  $\gamma$ -aminobutyric acid (GABA) and glutamic acid (GLU). Radioligand binding techniques had become popular in the 1970s and were used extensively in the 1980s in an effort to explain the chronic effects of antidepressants and to elucidate the interactions of benzodiazepines with GABA. There were concerns about whether these binding studies were physiologically relevant, and in some cases the chronic and acute studies on antidepressants were conducted in parallel with behavioural studies based on pharmacological challenges with drugs known to act on the receptors under investigation.

The radioligand binding studies (using membrane-enriched homogenates and also using autoradiography) led to proposals for receptor subtypes for NA, 5-HT, DA, GABA and GLU beyond those which had been proposed based on more classical physiological and pharmacological techniques. These studies led to the development of a number of drugs more specific for receptor subtypes than many of those previously available. *In vitro* binding studies were also being used by researchers such as Pavel Hrdina to investigate binding sites for antidepressants on platelets and by Phil Seeman and his group to provide evidence for multiple DA receptor subtypes, to explain the potency of antipsychotics and to shed further light (using studies in postmortem brain tissue) on possible DA receptor changes in schizophrenia. Studies on receptor subtypes were enhanced by the subsequent application of molecular biological techniques.

Electrophysiological studies conducted by Claude de Montigny, Pierre Blier, Jacques Bradwejn and colleagues also did much to enhance our knowledge of the mechanisms of action of antidepressants and provided the preliminary work suggesting cholecystinin's involvement in anxiety disorders (an area that was pursued very actively in the 1990s). The SSRIs, the first group of antidepressants specifically synthesized to act selectively on the uptake system for a neurotransmitter, were introduced clinically in the mid-to-late 1980s and subsequently revolutionized the treatment of depression and anxiety; in the 1980s the SSRIs were included in numerous basic science studies on mechanisms of action in antidepressants. Simon Young continued his studies on tryptophan metabolism by pioneering work on the tryptophan depletion model of

depression that was to be used so extensively in the 1990s.

Endocrinology studies on the HPA axis in depression flourished in the 1980s, leading to hypotheses on the role of glucocorticoid receptors in depression (e.g. Nick Barden) and to research on corticotropin-releasing hormone that would be prominent in the 1990s. Studies on interactions involving stress, the immune system and psychiatric disorders conducted by Canadians such as Hymie Anisman and Michael Meaney laid the basis for research on immunological aspects of mental health which has stimulated great interest in the 1990s and 2000s.

Advances made in the 1980s on intracellular messenger systems such as those involving G proteins (e.g. Ram Mishra) and inositol phosphates (e.g. Husseini Manji) and on immediate early genes such as *c-fos* (e.g. Harry Robertson) further increased our knowledge of the mechanisms of action of psychotropic drugs. Studies on trace amines such as 2-phenylethylamine, tryptamine, tyramine and octopamine, which had stimulated interest in the 1960s and 1970s, continued to be of interest in the 1980s due in large part to the availability of suitably sensitive and specific techniques such as high resolution mass spectrometry for measuring these amines in brain and to the application of electrophysiological and behavioural methods to studies on these substances; much of this work was done by Alan Boulton and colleagues. There was also increased interest in the role of peptides in psychiatric disorders (e.g. Remi Quirion) and the co-localization of some of these peptides with other neurotransmitters/neuromodulators.

Comprehensive metabolism and drug-drug interaction studies, at both the basic science and clinical levels, on antidepressants, anxiolytics and antipsychotics were conducted in laboratories such as those of Kam Midha in Saskatoon, Glen Baker and Ron Coutts in Edmonton and Werner Kalow and Ed Sellers in Toronto. Findings by the Toronto group and by numerous other researchers worldwide on isozymes of cytochrome P450 laid the foundations for future studies on pharmacogenetics and drug-drug interactions and made clinicians, industry and regulatory agencies much more cognizant of the importance of pharmacokinetic drug interactions involving psychotropic drugs. There was also considerable interest in the fact that many psychotropic drugs have one or more chiral centres but are marketed as racemates rather than individual enantiomers; interest in this area increased markedly in the 1990s.

Studies on acetylcholine and  $\beta$ -amyloid conducted in the 1980s [e.g. at the Douglas Hospital Research Centre (e.g. Remi Quirion) and the Department of Pharmacology at McGill (Claudio Cuello)] and a large number of other research centres worldwide led to a greater understanding of the neurochemistry of Alzheimer's disease and to a flurry of research activity in this disorder in the 1990s. Some of these studies were done on postmortem brain tissue, and similar studies on such tissue also led to marked advances in research on other psychiatric and neurologic disorders such as schizophrenia, Parkinson's disease and Huntington's chorea.

Development of suitable animal models for studying psychiatric disorders has always been a problem. In the past decade or so, research on animal models has pushed forward markedly with the use of genetically modified animals and the development of drugs which are selective for certain receptor subtypes, but in the 1980s, much was learned about reward mechanisms (Chris Fibiger and Tony Phillips, Franco Vaccarino, Andy Greenshaw, Rick Beninger), about the neurochemistry of psychiatric disorders, and about screening for antidepressants, anxiolytics and antipsychotics using animal models developed or refined in that decade. Phillips and Fibiger combined their behavioural studies with voltammetric techniques, and such studies were the forerunner of combined behavioural and *in vivo* microdialysis experiments that were used frequently in the 1990s. Canadian scientists such as Roy Wise, Bill Corrigan, Jane Stewart, Paul Clarke and Dave Roberts used animal models extensively to study mechanisms of action of addictive drugs.

In summary, numerous basic science advances in neuropsychopharmacology were made in the 1980s in areas such as mechanisms of action of psychotropic drugs, the etiology of psychiatric and neurologic disorders, pharmacogenetics, endocrinology, behavioural pharmacology, signal transduction and drug metabolism. Canadian neuroscientists were prominent in a great deal of the exciting research conducted in this decade, and the techniques involved and the knowledge gained were used to great advantage in the subsequent two decades.

One of the areas of neuropsychopharmacology research in which members of the College held a high profile of contributions was in schizophrenia, one of the more serious mental illnesses. The following is an overview of the personal experiences of Drs Mary and Philip Seeman who have contributed significantly to the understanding of the illness and its biological substrates.

### **SCHIZOPHRENIA RESEARCH IN CANADA, 1964-2004**

Philip Seeman, M.D., Ph.D. and Mary V. Seeman, M.D.

While one of us (Philip) was earning his Ph.D. at Rockefeller University in the early 1960s, the other (Mary) was conducting LSD experiments with her many patients at Manhattan State Hospital, while trying to learn to be a psychiatrist. Philip worked on red blood cells – basic work with no immediate clinical relevance. Mary one day said to Philip: “Why don’t you do something useful? Why don’t you help me with my patients? Why don’t you study schizophrenia?” That gentle prod produced results that would lead to the dopamine hypothesis of schizophrenia. In the 1960s, no one agreed on what schizophrenia was. Inclusion criteria varied so much that it was impossible to decide which patients to study, let alone what to study. But everyone seemed to agree that chlorpromazine and the many antipsychotic drugs that subsequently evolved helped the symptoms of schizophrenia, however defined.

I (Philip) wanted to know how these drugs worked so I started searching for an antipsychotic drug receptor site, first on red cell membranes, then in the brain. Most neuroscientists said I was wasting my time on that strategy. What seemed to be productive were epidemiological studies (Alexander Leighton and Jane Murphy, Roger Bland, Morley Beiser). A very effective strategy was studying children of parents with schizophrenia brought up at home versus those fostered or adopted (Jock Cleghorn, Duncan MacCrimmon, Richard Steffy, Robert Asarnow). The McMaster group was looking at growth hormone responses in those with schizophrenia (Greg Brown, Henry Szechtman). And clinicians, inspired by the pioneering work of Heinz Lehmann, were studying the effects of antipsychotic drugs on patients’ symptoms and functioning (Tom Ban, Gerry Sarwer-Foner, and later Yvon Lapierre and Guy Chouinard).

But I (Philip) was less interested in the global effect of these drugs than in a specific antipsychotic receptor, a site in the brain that responded to the very low concentrations of drugs to which humans were exposed during effective treatment. In 1972, I asked Paul Janssen (the inventor of haloperidol and many other medically important drugs) to synthesize radioactive haloperidol for me. Then, using a pair of mirror-image antipsychotic drugs, (+)- and (-)-butaclamol (the first being actively antipsychotic, the second not), to define the specific binding of radioactive haloperidol, my lab developed a receptor test for the antipsychotic receptor. This site turned out to be a dopamine receptor, D2, the common site of action for all of the known antipsychotics, including clozapine, quetiapine, and aripiprazole.

Dopamine functions began to be actively investigated in schizophrenia by Canadian researchers such as S. Lal, N.P.V. Nair, R.K. Mishra, T. Di Paolo. I (Mary), along with many

others (R. Yassa, G. Remington), turned my attention to the clinical side effects caused by the dopamine blocking action of antipsychotics.

Philip found an excellent correlation between the haloperidol binding site in brain tissue and the average clinical doses of neuroleptics. The summer of 1974, in Paris at an evening garden party for the CINP, Philip rushed up to Paul Janssen to tell him the good news. Paul Janssen laughed and said that averaging the clinical doses was like averaging all the religions in the world. Nevertheless, the correlation remains a cornerstone of the dopamine hypothesis of schizophrenia, still the major contender for an explanatory theory of schizophrenia causation. Hubert Van Tol and Chaim Niznik, together with Philip, cloned many dopamine receptors (D1, D2short, D2Longer, D4 and D5) and were active in studying the molecular biology and properties of dopamine receptors.

Diagnosis had improved and, by the 1980s, structural and functional imaging was being used to test etiological theories (Jock Cleghorn, Bob Zipursky). After Philip published in *Science* that dopamine D2 receptors were elevated in post-mortem schizophrenia brain tissues, Dean Wong at Johns Hopkins, using brain imaging with radioactive methylspiperone, reported in 1986 that D2 receptors were elevated in schizophrenic patients who had never ever been treated with antipsychotic drugs. The alterations of dopamine D2 receptors in various brain regions continues to be examined by PET. Clinical brain imaging is now driving much of the basic science of schizophrenia. The Vivian Rakoff Brain Imaging PET facility at the University of Toronto has a range of research clinicians actively working to find the mechanisms of action of antischizophrenic drugs and the etiology of schizophrenia (Sylvain Houle, Alan Wilson, Shitij Kapur, Bob Zipursky, C. Shammi, Gary Remington). Unfortunately for schizophrenia research in Canada, two leaders in the field, Jock Cleghorn and Chaim Niznik, died prematurely and left a gap that is not easy to fill.

Shitij Kapur and I (Philip) have used radioreceptor assays and brain imaging to try to understand why the newer antipsychotic drugs do not produce extrapyramidal symptoms and tardive dyskinesia. The CCNP in 2004 awarded us with an Innovation award for our work showing that clozapine and quetiapine act on D2 receptors in this “atypical” way because they bind loosely to the receptor and allow the free transmission of endogenous dopamine. The CCNP has been especially considerate to me, after earlier giving me the Heinz Lehmann Award for Schizophrenia Research and, more recently, conferring Honorary Membership in the CCNP.

In recent years, neuropsychology has become increasingly important to schizophrenia studies since cognitive symptoms produce as much impairment, if not more than, psychotic symptoms. Active in this area are Bruce Christensen, Jean Addington, Jeff Daskalakis, Emmanuel Stip, aided by new technology such as transcranial magnetic stimulation. The search for genetic mechanisms responsible for schizophrenia has been intense, and Canadian researchers are leading the way (Jim Kennedy, Anne Bassett, Bill Honer, Marcel Maziade, Art Petronis, Teresa Tallerico). Areas on several chromosomes are being investigated and epigenetic mechanisms show promise.

Ever new technology such as functional MRI (Peter Williamson) is helping to uncover the pathogenesis of this mysterious illness. At the same time, clinical research addressing quality of life, male/female differences, and the benefits of early intervention (George Awad, Mary Seeman, Lili Kopala, Jean and Don Addington, Bob Zipursky, Ashok Malla, Ross Norman) is making life for patients more meaningful. In the last 40 years, diagnosis has become more reliable, pathogenesis is better understood, treatments are more effective, families are no longer being blamed, and the stigma of schizophrenia has lessened. Canadian researchers have been at

the forefront of all these developments.

### *Journal of Psychiatry & Neuroscience*

The Psychiatric Journal of the University of Ottawa was started in 1975 by Dr G.J. Sarwer-Foner, the newly appointed chairman of the Department of Psychiatry. It was a general psychiatry publication and was supported financially mainly by sustaining subscriptions paid by members of the department. Its survival as a general psychiatry journal of regional origin was becoming precarious without the regular financial input from the department.

A new business plan was developed under the direction of the new chairman, Y.D. Lapierre, in the late 1980's. It was renamed "*Journal of Psychiatry & Neuroscience*" and a new financial structure was established so that it would become self-sustaining. The mission of JPN was refocused to serve as a conduit of research and knowledge communication between clinical and basic sciences.

In May 1990, discussions with the CCNP were initiated with the objective of JPN becoming the official organ of the CCNP in its communications with the scientific world. The editorship of the JPN felt that there was a distinct need for a Canadian publication in neuropsychopharmacology and decided to proceed forthwith in the development of the new publication.

The CCNP was somewhat hesitant to make a commitment of ownership in such a venture but was interested in the concept of having such a medium available. An ad hoc Journal committee of the College consisting of Alan Boulton, Greg Brown, Pavel Hrdina, and Remi Quirion was established under the chairmanship of Dr Andre Villeneuve and mandated to discuss and negotiate with Yvon Lapierre, editor-in-chief of JPN.

In March 1991, the JPN started publishing under its new name. The editorial board was restructured with Y. Lapierre as editor-in-chief and Terry Pivik, Pavel Hrdina and Simon Young as co-editors with a number of actively participating associate editors. The Canadian Psychiatric Association was contracted as publisher for a period of three years. The CCNP adopted JPN as its official organ the following year with the understanding that the College would have the major role in the selection of the editorial board.

At the end of the three-year arrangement, JPN was sold to the Canadian Medical Association that was interested in developing the range of its publications in the area of mental illness and associated brain disorders. The role of the CCNP was maintained as previously. After a period of transition, Yvon Lapierre retired as editor in chief and was succeeded by two co-editors in chief, Simon Young and Russell Joffe, as the CCNP's nominees. This arrangement resulted in solidifying the role of the JPN in the scientific community with increased citation index scores on a quasi-annual basis. It is now recognized as one of the leading publications in neuropsychopharmacology.

### *Epilogue*

Institutional memory is fragile and is easily lost. This write-up of the initial years of the CCNP was initially suggested to me by Dr George Awad during one of the annual scientific meetings. At that time, he suggested that I write my recall of the events leading up to and during the early years of the College with the collaboration of colleagues who had also participated. He mentioned "en passant" that it was time to do it while there were sufficient numbers still alive or able to do so. This reality stuck with me as a short time thereafter I was personally faced with a life-threatening event. I started organizing the material for the write-up with an understanding

from Pavel Hrdina that he would assist once the first draft was done. Once partly completed, Pavel received an initial draft along with the news that he was now afflicted by a second cancer with a short expectancy of survival. This sad news was demoralizing to me and brought the work on the CCNP history to a standstill for quite some time.

The loss of other early collaborators such as Bill Dewhurst, Jock Cleghorn, Sam Lal, Bish Saxena, Joe McClure and most recently Alan Boulton now acted as a stimulus for a new sense of urgency so that the recall of the early years of the CCNP would not be totally lost. It is obvious that this is not a historical document but a reference for those who may be interested in the early years of neuropsychopharmacology in Canada to allow them to develop some feel of those years. We are now past the times when a psychiatrist who espoused the opinion that mental illness had a strong biological basis and could effectively be treated by medical procedures was ostracized from the mainstream of academic psychiatry. The developments in neuropsychopharmacological research described in this monograph should be viewed in the context of gradual insertion of scientific method in the evaluation and treatment of mental disorders.

Hopefully, the presence of the CCNP in the Canadian environment of researching and treating mental illness has and will continue to improve the quality of life of those afflicted by the illness as well as their families. Now that I have had a few years on the sidelines as an observing and interested retiree, I close this by simply concluding that this epilogue is but the prologue of what is yet to come.

Yvon D. Lapierre, M.D.

#### Collaborating contributors

A. George Awad, M.D., Ph.D.

Glen B. Baker, Ph.D.

Guy Chouinard, M.D.

Mary Seeman, M.D.

Philip Seeman, M.D., Ph.D.

Theodore Sourkes, Ph.D.