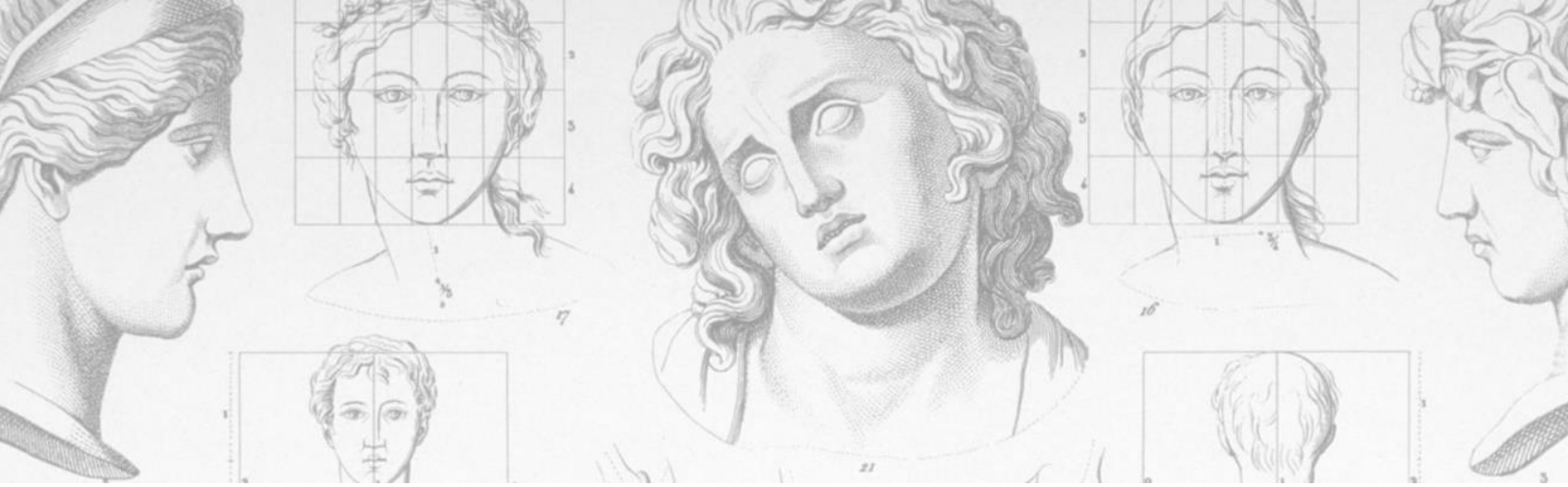

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Patrick L. McGeer and
Edith Graef McGeer

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Patrick L. McGeer

BORN:

Vancouver, British Columbia
June 29, 1927

EDUCATION:

University of British Columbia, B.A. (1948)
Princeton University, Ph.D. (1951)
University of British Columbia, M.D. (1958)

APPOINTMENTS:

Research Chemist, duPont Co., Wilmington, Delaware (1951)
University of British Columbia (1956)
Professor Emeritus, University of British Columbia (1992)

HONORS AND AWARDS:

Outstanding Alumni Award, University of British Columbia (1994)
Officer, Order of Canada, Canadian Government (1995)
Special award for lifetime contributions, B.C. Science Council (1995)
Distinguished Medical Research Lecturer, University of British Columbia (1998)
Beaubien Award of Excellence, Alzheimer Society of Canada (1998)
Alumni Research Award, University of British Columbia (1999)
Honorary D.Sc., University of British Columbia (2000)

Edith Graef McGeer

BORN:

New York, New York
November 18, 1923

EDUCATION:

Swarthmore College, B.A. (1944)
University of Virginia, Ph.D. (1946)

APPOINTMENTS:

Research Chemist, du Pont Co., Wilmington, Delaware (1946)
University of British Columbia (1954)
Professor Emeritus, University of British Columbia (1989)

HONORS AND AWARDS:

Honorary Fellow, North Pacific Society of Neurology and Psychiatry (1960)
Distinguished Medical Research Lecturer, University of British Columbia (1982)
Honorary D.Sc., University of Victoria (1987)
Officer, Order of Canada, Canadian Government (1995)
Special award for lifetime contributions, B.C. Science Council (1995)
Outstanding Non-Alumni Award, University of British Columbia (1996)
Honorary D.Sc., University of British Columbia (2000)

Patrick and Edith McGeer carried out fundamental work in neurochemistry and neuropharmacology. They mapped the cholinergic system of the brain, described the distribution of GABA neurons, and demonstrated a neurotransmitter role for glutamate. They also demonstrated the loss of cholinergic neurons during normal aging, exploited excitotoxic drugs to develop an animal model of Huntington's disease, and were among the first to suggest that antiinflammatory drugs might reduce the prevalence of Alzheimer's disease.

Patrick L. McGeer and Edith Graef McGeer

Early Years

Patrick McGeer was born in Vancouver, the youngest of three children of Judge James McGeer. His mother Ada worked as a radio producer for the Canadian Broadcasting Corporation. Although there was no family tradition of science, both Pat and his older brother Peter felt the allure. Pat went to the local public schools and then to the University of British Columbia, where he graduated with first class honors in chemistry in 1948. Still, his major interest as an undergraduate was not chemistry but basketball. His high school friends formed the core of a team that matured into a northwest basketball powerhouse. They beat the Harlem Globetrotters in 1946, then considered to be the number one team in the world. His team went on to represent Canada in the 1948 Olympic Games. Pat was an all-star and conference scoring champion. Pat recalls that he drifted from premedicine into chemistry and physics, mainly because the courses seemed easy, leaving lots of time for sports. After winning the Canadian University Basketball Championship in 1948, Pat visited his elder brother Peter, who was completing his Ph.D. in chemistry at Princeton. Dean Hugh Taylor offered Pat a scholarship at Princeton, mostly on his brother's reputation. Expectations were modest: 'We are really scraping the bottom of the barrel this year,' he said to Pat.

Pat returned from the 1948 Olympics in London to commence graduate work. Princeton University was an inspiring place, steeped in intellectual tradition, and then populated with legendary scientific figures. Albert Einstein and John Von Neumann were at the Advanced Institute, Eugene Wigner and Henry Smythe were in the physics department, and Hugh Taylor (later Sir Hugh) and Henry Smythe's younger brother Charles (Pat's supervisor) were in the chemistry department. Students soon learned that their mentors were leaders in their fields. Here was a grounding par excellence in the scientific method. Pat shared a laboratory with George Rathmann, later to become the first employee of AMGEN and a legendary figure in the biotechnology industry. They both worked on microwave absorption in dielectrics, using klystrons developed in World

War II. A major nuisance was water vapor absorbing 3-cm waves, but neither thought of the obvious application: Microwave ovens were left to someone else's devising!

The graduate students lived in the relative luxury of the Graduate College. It was situated on a golf course a short distance from the main campus. The undergraduates referred to it as 'Goon Castle' and, on a football Saturday teeming with alumni, planted a huge sign at the entrance: 'Please do not feed the Graduate Students.' To Pat, the 'goons,' then as now, were an awesome collection of intellectual talent. He considered it a humbling but exciting experience to be among them.

Completing his Ph.D. in physical chemistry in 1951, Pat went to work in the Polychemicals Department of duPont in Wilmington, Delaware. The salary seemed huge. He promptly invested in a secondhand car and became part owner of a small boat and a small plane. His successors in Smythe's lab eagerly informed his former supervisor of this acquisitive lifestyle. When he returned to Princeton on a visit, Smythe, with typical wry humor, remarked, 'Well, Pat, you have lots of transportation, but where are you going?'

Edith was born in New York as the youngest child of Dr. Charles Graef, an eye, ear, nose, and throat specialist, and Charlotte Graef (nee Ruhl), a housefrau from a German family in which all the men for at least two generations had been physicians. Edie attended a small private school in New York and then Swarthmore College on an Open Scholarship. Always intrigued by science, she had a traumatic introduction to Swarthmore. When she went to get her course card signed by the head of the chemistry department, the crusty old gentleman gave her a half-hour lecture on how she was wasting her time and, more important, his time because women could not do chemistry! However, she persisted. The younger professors were more supportive and even the head thawed when the male students were mostly pulled out in 1943 and he had to turn to Edie for help as an assistant in the freshman laboratory. Edie was not as athletic as Pat but did manage to acquire her letters in both golf and badminton. Edie left Swarthmore in 1944 with a B.A. in chemistry and a Phi Beta Kappa to move on to the University of Virginia, where she worked on the synthesis of possible antitubercular agents under Dr. Alfred Burger.

The Jefferson-built University of Virginia was a charming environment, but Edie believed she got her best training during her undergraduate years rather than in graduate school. The people at Virginia had asked her to come early in the belief that she would have to make up for the years spent at Swarthmore. However, the reality proved far otherwise; Edie had been so well trained at Swarthmore that she left Virginia 2 years later, in September of 1946, with a Ph.D. in organic chemistry and a Lychnos Society honor award, to take up a position with the duPont Company. She attributes her development at Swarthmore to the fact that juniors and

seniors in honors learned through a system of reading and small discussion groups; there were no lectures. Although winning teaching awards for her own lectures, Edie has always believed that the lecture system was outmoded by the invention of the printing press—it has just refused to die.

Young scientists were very fortunate in those days because they were in short supply in both industry and academia, and every graduate had several job offers from which to choose. Edie chose duPont because she liked both the type of job she was offered and the honesty of the company representative. Several other companies that offered her a job had said she would receive equal treatment with the men, but none could point to any woman in a supervisory role. The duPont representative said Edie would receive equal treatment with regard to pay and bonuses but would not be moved into the managerial stream because the company could never be certain that she would not get married and leave abruptly, which, of course, is exactly what happened.

E. I. duPont and Our 'Unlikely' Meeting

E. I. duPont de Nemours stood at the pinnacle of industrial chemistry in the early postwar years. The company was hiring one-half of all chemistry Ph.D. graduates in the United States. Its sprawling new Experimental Station in Wilmington was like a huge university campus with nothing but chemistry buildings. The company's organic chemists, led by the legendary Wallace Carothers, had, during the 1930s, worked out the basic principles of high-polymer chemistry. Nylon was his gem, inspiring the company slogan 'Better things for better living—through chemistry.' DuPont was simply 'The Company' and the scientists were made to feel like members of a large family. Bordering the Experimental Station was the DuPont Country Club with many tennis courts and 36 holes of golf, a fringe benefit provided to duPont workers at low cost.

Among the products Pat worked on developing was Teflon. Its discovery was serendipitous. A chemist, opening the valve on a tank of tetrafluoroethylene, found no gas escaping. Instead of simply looking for a new cylinder, he checked the weight. There was no weight loss from the last recording. He decided to saw through the thick metal walls. At the bottom was some light flaky powder. It turned out to be Teflon, with all its amazing properties. The Polychemicals Department worked on plastics, but Pat's supervisor Bill Gore thought Teflon would make an excellent fiber. The powers that be disagreed. They told Bill to forget about developing Teflon as a textile or leave the company. Therefore, he left the company and gave the fiber his own name—Gortex. A huge new company was borne.

Edie worked in the Intelligence Division of the Chemicals Department, which was supposed to do the basic research for new lines of chemicals. The Intelligence Division was also supposed to dream up ideas! Her only

major achievement during those years was suggesting a synthetic route to tetracyanoethylene. The synthesis was accomplished by Dick Heckert, a later president of the duPont Company but then a lowly chemist in the Chemicals Department. Tetracyanoethylene proved to be highly reactive, losing one cyano group to link with almost any compound having an active hydrogen that could be replaced. The synthesis led to a whole new branch of organic chemistry. It meant patents and citations from the American Chemical Society for both duPont and Edie, but it never produced commercial products for the company.

Pat worked at duPont for more than 2 years without crossing paths with Edie, even at the duPont golf courses. Dick Hagen, one of Pat's bachelor pals and a private pilot, approached him at the club one evening and asking if he wanted to buy a plane. 'Yes, of course,' Pat replied, not knowing how to fly. Hagen, Pat, and his roommate Maurice Hall bought a small Aeronca for the princely sum of $750. Maurice could not fly either. They went to pick up the plane at a small field in Maryland and, although the plane seemed a little low on gas, the next airfield was just a short distance away. Hagen took off with Pat in the passenger seat. Unfortunately, the plane ran out of gas and had to glide to the nearby airport. Word spread like wildfire around the Experimental Station. Three nuts had bought an airplane, only one of them could fly, and the first thing they did was run out of gas. Should people at the Experimental Station start wearing hard hats whenever they went outside? Edie's mother, a worrier who was fiercely protective of her children, extracted a solemn promise from her daughter that she would have nothing to do with this dangerous trio. However, chance dictated otherwise. A new apartment building was completed very near the Experimental Station, and who should move into apartments across the hall but Edie on the one side and the two plane owners who could not fly on the other. It took Pat only a few weeks to realize he was on the wrong side of the hall. And so we married, Pat moved across the hall, and a collaboration began that at this writing is in its 46th year.

Edie remembers fondly the week in February when they became engaged. As she wrote her mother, then in Florida: 'Last week was quite a good week. I won the duPont women's Ping-Pong tournament on Sunday, my partner and I won the duplicate bridge match on Tuesday, and I got engaged on Thursday.' Surprisingly, Edie's mother never mentioned Ping-Pong or bridge in the frantic phone call that immediately followed.

During the 2 months of our engagement it was time to think of a life together. Would it be in the comfortable confines of duPont or were there new horizons to explore? Pat had applied to medical school at the University of British Columbia (UBC) before he met Edie and had been accepted for the fall of 1954. With the long tradition of medicine in her family, Edie believed Pat would not be happy unless he had a chance to

pursue this long-desired career. Therefore, we decided to quit duPont and moved to Vancouver in June in order to get settled before medical school began in the fall.

Medical School at the Dawn of Neuroscience

When we moved to Vancouver in 1954, the Society for Neuroscience did not exist. There was not even a field of neuroscience. There was no field of neuropharmacology, no field of molecular neurobiology, and no field of neurochemistry. Neuroanatomy and neurophysiology were well established, but they operated as separate entities. Transmission between neurons was presumed by teachers of neurophysiology to be electrical. Watson and Crick had just reported on the structure of DNA but this had not reached the teaching level, at least at UBC's medical school. Nucleic acids were simply mysterious molecules.

Within the next decade, there was an explosion of scientific discoveries about the operation of the brain. The foundations for neuropharmacology, neurochemistry, and molecular neurobiology were established during this period as well as their need for integration into the broader field of neuroscience. The Society for Neuroscience was created in 1970 near the end of this formative period. Part of its purpose was to promote such integration. We were two of the few hundred who attended the initial neuroscience meeting in Washington, DC in 1971. Pat was so impressed by the prospects of the new society that he immediately organized a British Columbia chapter, the first in Canada.

It is difficult to recreate the excitement of those formative years. A mystery novel is boring for the reader who has already been thoroughly briefed on the plot. However, to scientists confronted by the wall of ignorance that existed at that time, the unfolding events had all the aspects of a genuine thriller. The events began with the almost accidental discovery of drugs with antipsychotic action. It was quickly observed that this action was coupled with extrapyramidal side effects. In completely unrelated investigations, it was found that the catecholamines and serotonin occurred in unusually high concentrations in brain. Closure began when it was found that the antipsychotics either blocked or depleted these amines. Dopamine was the only amine to be highly localized in the striatum. Its precursor L-DOPA was found to overcome the akinetic effects of reserpine. Then it was discovered that dopamine was depleted in the striatum of parkinsonian patients and that lesioning of the substantia nigra depleted striatal dopamine. Meanwhile, neurophysiologists were developing intracellular recording techniques that caused them to reject the notion that neurotransmission in the central nervous system (CNS) was electrical. Chemical messengers must exist. When Dahlstrom and Fuxe demonstrated serotonin and catecholamine pathways in the CNS, the

neurotransmitter era was launched, with neuropharmacology focusing on synaptic biochemistry.

As in many fields of science, the initial findings were serendipitous. Delay and Deniker reported in 1952 that chlorpromazine, which had been introduced into medicine as a treatment for intestinal worms and then utilized as an antihistamine and basal anesthetic, had a tranquilizing effect on schizophrenics. At about the same time, reserpine, derived from the ancient Hindu herbal medicine rauwolfia serpentina, was introduced as an antihypertensive agent. It was also noted to have a tranquilizing action. As a medical student, Pat was occasionally at Essondale, the huge British Columbia mental sanitarium, at the time these agents were first being administered to schizophrenics. The results were magical. Straitjackets went into storage, padded cells were emptied, and the music in the trees, which dulled the yelling from the most disturbed patients, was turned off. The rows of beds with convulsing patients being tube fed concentrated sugar solutions following insulin shock treatment disappeared. The wards were converted from places of bedlam to quiet residences. We wondered what could possibly be the special brain biochemistry that lay behind these changes.

We were fortunate in those formative years to come in contact with Dr. William C. Gibson. He was one of the brightest lights in the recently established medical school. He had been a student of Wilder Penfield at the Montreal Neurological Institute. Penfield had sent him to Oxford to work with Sir Charles Sherrington in his final years. Gibson developed silver staining methods for boutons, and Sherrington suggested he go to Madrid for further study under Del Rio Hortega. This was a short-lived relationship due to the outbreak of the Spanish Civil War. He subsequently studied at Yale with the great physiologist John Fulton. He knew all the nervous system luminaries at the time he set up neurological research at UBC. The unit was sponsored by Essondale Hospital, so there was a special interest in mental disease. He was anxious to apply chemical techniques to an understanding of psychiatric problems and, due to our background in chemistry, we fitted well with his plans. William Gibson was an indefagitable facilitator who quickly led us to the frontiers in those early days. He was an inspiration for us then and continues to be to this day. Pat started working in his laboratory during the summers and Edie part-time as a volunteer while our own family was in its infant stages. However, there was not much time for research. Medical school is demanding, and there was also the extremely enjoyable complication of the arrival of our children: Rick in 1957 (now a computer scientist), Tad in 1958 (now an aeronautical engineer), and Tori in 1960 (now a philosopher). Each took a Ph.D. in their field, but they avoided medical science, having received enough of it around the dinner table as children.

A few memories remain from those days about the odd new field we were embracing. Bill Gibson sent Edie in early 1956 to a meeting of psychiatrists in Chicago. It was much smaller than an American Chemical Society meeting and much different in tone. Edie still remembers listening for what seemed like hours to a hot debate as to whether monkeys could have an Oedipus complex. We both remember driving back with Bill Gibson from our first meeting with psychiatrists at the mental hospital. We were giving polite responses to Bill's questions about our impressions when he remarked in a meditative tone, 'Oh well, there's no reason why a person with a diseased hip can't be an orthopedic surgeon.'

Hoffer, Osmond, and Smythies introduced the term 'hallucinogen' to describe compounds with opposite effects to the tranquilizing agents. These were compounds such as LSD and mescaline that would induce bizarre mental changes while, like the tranquilizing agents, having little effect on the periphery of the body. In those days, hallucinogens were not street drugs but scientific curiosities. Hoffer, Osmond, and Smythies developed the theory that schizophrenia was caused by abnormal metabolism of adrenaline, forming a compound they called adrenochrome, which mimicked the hallucinogen mescaline. John Smythies moved from Hoffer's laboratory in Saskatoon to work with Dr. Gibson on silver staining of boutons. He introduced Dr. Gibson to the hallucinogenic theory of schizophrenia. Dr. Gibson wanted a chemist to measure the levels of adrenochrome in schizophrenic and normal urine. Edie synthesized some adrenochrome and found it so unstable in urine that it disappeared within a few seconds, which ended that approach. Nevertheless, it seemed at the time that the answer to schizophrenia was just around the corner. That corner is yet to be turned, and a metabolic abnormality remains an attractive hypothesis almost half a century later.

The introduction of tranquilizing agents immediately began to focus attention on the overlap between mental disorders and extrapyramidal function. Although chlorpromazine and reserpine relieved psychotic symptoms, they induced prominent parkinsonian side effects. What sort of chemistry produced this overlap?

The answers were to emerge from investigations of a group of aromatic compounds that became known as the biogenic amines. Martha Vogt reported in 1954 that 'sympathin' (noradrenaline) existed in relatively high concentrations in the midbrain and hypothalamus, which could not be explained on the basis of vascularity. The previous year, Twarog and Page found an unusually high concentration of serotonin in brain. Shortly after, Amin, Crawford, and Gaddum reported the highest concentration to be in the hypothalamus and limbic system. Woolley and Shaw proposed that either an excess or deficiency was responsible for mental illness. Pletcher, Shaw, and Brodie began to provide closure by noting that reserpine depleted serotonin from the gut, which was followed by reports

showing that it reduced noradrenaline and serotonin from all tissues of the body, including brain.

The stage was now set for Arvid Carlsson's classic experiments. He took advantage of the recent invention of the spectrophotofluorometer to develop an analytical method for dopamine. Carlsson found that extraordinarily high concentrations of dopamine occurred in the corpus striatum, and, like the other catecholamines and serotonin, it was depleted following the administration of reserpine. This correlation between high levels of dopamine in the corpus striatum, its depletion by reserpine, and the accompanying parkinsonian-like side effects led Carlsson to propose that dopamine was involved in extrapyramidal function. Carlsson showed that the akinetic state of reserpine-treated rabbits could be remarkably overcome by systemic administration of the dopamine precursor L-DOPA. Prior to that time, dopamine was considered to be merely an inactive precursor of noradrenaline and adrenaline.

Birkmeyer and Hornykiewicz followed up on the hypothesis of Carlsson by measuring dopamine levels in autopsied brains of a series of parkinsonian patients. They found that there were sharply decreased levels in the striatum. A connection was thus made between Parkinson's disease, dopamine, and the pharmacological actions of reserpine.

Despite the establishment of these relationships, there were puzzling aspects. Dopamine and serotonin were uniquely distributed in brain. However, what could be their function? They could not be established as neurotransmitters in the periphery. The puzzlement was compounded by the knowledge that neuronal loss in Parkinson's disease was in the substantia nigra and not in the striatum.

The Early Postmedical School Years

In the late 1950s, we believed the biogenic amines must be central neurotransmitters but felt we had to acquire new skills to enter the field. Radioactive compounds of high specific activity were then becoming available, and this was a way of tracing what occurred in small areas of brain. Following internship, Pat had been immediately offered a faculty position in the UBC medical school. To become experienced in the new methodology, we arranged to spend 4 months at the Worcester Foundation before starting faculty duties. It was an exciting place for many reasons: The day we arrived, Hudson Hoagland handed us a paper by his colleague Gregory Pincus that had just appeared. 'Read this,' he said, 'it may have long-term implications.' It was a report of the clinical trial that had just been completed in Puerto Rico of their birth control pill. Gregory Pincus would later win the Nobel prize for this work, which has had widespread social ramifications. After a brief but stimulating period during which we learned to handle radioactive isotopes, we

returned to Vancouver in January 1960 ready to commence research on a full-time basis.

At that time, Hugh McLennan had joined UBC in the Department of Physiology. Hugh had worked with Florey and Elliott in McGill on GABA as a possible inhibitory neurotransmitter. Their test system was the crayfish stretch receptor neuron. We suggested that Hugh test dopamine in this system because of its GABA-like atomic structure. Dopamine proved to be 80–100 times more active than GABA. The activity of dopamine, but not GABA, was blocked by chlorpromazine. These results suggested that dopamine did have neurotransmitter potential and that its receptors were different from those of GABA. This work was published in 1961.

It later proved that the discovery was serendipitous. Hugh was pilloried for many months by other physiologists who had tried to duplicate the results with dopamine without any success. Finally, several physiologists got together with their crayfish and samples of dopamine and discovered that only the Pacific crayfish that Hugh had used was responsive. All other species of crayfish showed no reaction to dopamine. Nevertheless, this was the first demonstration of a neurotransmitter-like activity of dopamine.

Following the earlier leads of Carlsson and Birkmeyer and Hornykiewicz, we tested whether oral DOPA would be effective in overcoming drug-induced extrapyramidal reactions in mental patients and the idiopathic extrapyramidal symptoms in parkinsonian patients. In both situations, only mild effects were noted, far less than were subsequently established by Cotzias with his careful and elegantly executed clinical studies. Cotzias shrewdly used L-DOPA, the true precursor of the catecholamines, rather than the less expensive DL-DOPA we had employed, and he did not use pyridoxal. The latter decision turned out to be critical. Pyridoxal is a cofactor for decarboxylase activity. We had added this cofactor to DL-DOPA because we were afraid the decarboxylation load would deplete stores of pyridoxal with deleterious effects on the liver. Unfortunately, this merely increased the peripheral decarboxylation. Now, of course, it has been established that peripheral decarboxylase inhibitors are required to maintain high levels of levodopa in the serum and thus provide sufficient quantities of this dopamine precursor to the brain. Decarboxylase inhibitors, which do not cross the blood–brain barrier, are included as part of all modern levodopa formulations.

We were aware that L-DOPA would be far preferable to the DL form and we knew it had originally been isolated from black-eyed beans, a cattle feed used in the southern United States, which contain an extraordinarily high concentration of L-DOPA. Therefore, we had a large sack of feed delivered to us. First, we broke several Waring blenders in an effort to

mash the beans to extract the L-DOPA. Then, Edie tried every culinary trick to make an edible dish from the whole beans without success. We eventually concluded that it was preferable to suffer from Parkinson's disease than mimic cattle by eating black-eyed beans.

The question was still not answered as to where brain dopamine was made and how it reached the striatum. Having learned to handle radioisotopes in Worcester, we started working on this problem by injecting labeled tyrosine into the striatum of rats and recovered labeled dopamine. Tyrosine was the precursor and tyrosine hydroxylase was present in the striatum. This result was published in 1963, the year before Nagatsu and Udenfriend purified tyrosine hydroxylase from adrenal tissue.

A great achievement came in 1964 when Dahlstrom and Fuxe published their mapping of dopamine, noradrenaline, and serotonin-containing neurons based on fluorescence histochemistry. They refined the histochemical fluorescence methodology, originally demonstrated by Eranko and further developed by Falck and Torp, to localize the amine-containing neurons and their projection pathways. At the same time, Poirier and Sourkes were lesioning the substantia nigra in monkeys and showing a decrease in catecholamine levels in the striatum. Thus, the nigrostriatal pathway, critically injured in Parkinson's disease, was the first neurotransmitter pathway to be demonstrated in brain.

Following the triumph of Dahlstrom and Fuxe in defining the catecholamine and serotonin pathways, it was clear that these materials were neurotransmitters, but they served only a tiny fraction of the brain's neurons. What were the other neurotransmitters and which neurons used them? The discipline of biochemical neuroanatomy was launched and was to occupy our attention for the next 20 years. There were many possible neurotransmitter compounds, but any candidate put forward was the subject of long and hot debate, with the chemists usually pro a neurotransmitter role and the physiologists usually anti. We remember leaving a meeting in California during this period in the company of Eugene Roberts. Gene shook his head sadly and said 'GABA went into that meeting this morning as a rich neurotransmitter candidate; it's coming out this afternoon as a poor metabolic relative.'

There was anticipation that great strides in the treatment of mental and neurological diseases would follow identification of these neurotransmitter substances. Synaptic biochemistry was barely scratched. A combination of neurophysiological and biochemical techniques seemed necessary to make progress. We turned to Jack Eccles as our mentor. He provided tremendous insight into the intricacies of synaptic function. Our collaboration was mostly from afar, but it resulted in our joint authorship of two editions of *Molecular Neurobiology of the Mammalian Brain* (1978, 1987).

Sir John Eccles

Sir John Eccles (1905–1998) was the most outstanding neurophysiologist of the twentieth century. He was a worthy successor to his mentor at Oxford, Sir Charles Sherrington (1857–1952). Sherrington, who conceived the synapse, was the most outstanding neurophysiologist of the nineteenth century. Hopefully, it will not be long before worthy biographies of Sir John (who wanted to be known to everybody as Jack) are written so that the neuroscientists of today can appreciate his great contributions. His discoveries were all the more remarkable in that they were made in remote locations in unlikely circumstances. He was overlooked for the chair at Oxford when Sherrington retired at the ripe age of 78. Poor Oxford—what a blunder! Jack moved to Australia to become director of the Japanese-financed Kanamatsu Institute. He was then appointed to the chair of physiology at the University of Otaga, located in Dunedin, New Zealand. It was here that he did his first intracellular recordings of postsynaptic potentials, discovering the inhibitory hyperpolarization of the postsynaptic cell that eventually led to his Nobel prize. When the Australian National University was established in 1952, Jack became professor of physiology and returned to his native land.

Our mentor, Bill Gibson, had overlapped with Eccles and Sherrington at Oxford, and they had become good friends. At Bill's invitation, Jack visited UBC in the late 1950s and early 1960s, giving riveting lectures on the organization of the nervous system and the role of excitatory and inhibitory synapses. We queried him at length as to how the newly discovered biogenic amines fitted into all of this. What about the pharmacological actions of chlorpromazine and reserpine, and the effects of L-DOPA that Arvid Carlsson had demonstrated? Jack quickly conceptualized the new data and translated these into experimental ideas for testing them as neurotransmitters. At that time, he knew he was up for the Nobel prize, which he won, along with Andrew Huxley and Allen Hodgkin, in 1963. Jack believed that he had been isolated during his years in Australia and New Zealand and wanted to move to North America where he would be closer to the mainstream of neuroscience. 'Would Jack possibly come to the University of British Columbia?' we asked. Would a different type of collaboration be possible where his knowledge of neurophysiology might be combined with contemporary neurochemistry? Alas, it was not to happen. Jack wished to move to the United States and took up a position created by the American Medical Association in Chicago. It was an unhappy period for him, and Jack moved on to the University of Buffalo. However, he accepted the post of visiting professor at UBC, which gave him the opportunity to pay regular visits. He enjoyed the Faculty Club (now closed), which he considered the best in the world, as well as visiting the many friends he had made in Vancouver. It was during these visits that we

conceived our monograph *Molecular Neurobiology of the Mammalian Brain.*

In the first edition, we defined the anticipated properties of neurotransmitters. Anatomically, they should occur in significant concentrations, be localized to synaptosomes, and suffer decreases if their axons were severed. Chemically, there should be enzymes for their rapid supply and disposal, there should be an uptake pump, and they should be released in a K^+-stimulated and Ca^{2+}-dependent fashion. Physiologically, they should show action at receptor sites following nerve stimulation or ionotophoretic application. Pharmacologically, agents should be identifiable that interfere with their synthesis, storage, release, or postsynaptic action or that mimic their physiological effects. These criteria have provided great guidance in defining neurotransmitter systems.

We assembled evidence concerning all of the then-known and suspected neurotransmitters. We gave a brief historical account of each as well as the contemporary evidence. They included the classical group of dopamine, noradrenaline, adrenaline, and serotonin; acetylcholine; the excitatory amino acids glutamate and aspartate; and the inhibitory amino acids GABA and glycine. We also mentioned putative candidates such as histamine and the 'promising peptides.' It was clear that these compounds did not all work in a similar fashion. Some definition was needed to explain the known diversity: Some neurotransmitters worked by opening ionic channels; others worked simply by binding to a postsynaptic surface, triggering a second messenger signaling agent intracellularly. How should we define this difference? We devised the concept of ionotropic to define all neurotransmitter actions that opened channels and the concept of metabotropic to describe all those actions that worked through second-messenger signaling. In the second edition to our book (1987), we extended this concept to include genotropic transmission, describing those actions that resulted in intracellular signals being translocated to the nucleus with actions on DNA transcription. These concepts have not been universally applied. Only for the glutamate receptors have the terms ionotropic and metabotropic received general acceptance. However, we believe the broader concept is still a useful way to view neurotransmission in the CNS.

Biochemical Neuroanatomy

We used a variety of techniques in our search for the pathways used by neurotransmitter candidates in the period 1962–1986—surgical lesions with measurement of the levels of the synthetic enzymes, axonal transport, histochemistry, immunohistochemistry, and kainic acid lesions. Since transmitters such as acetylcholine are unstable, we concentrated on localizing the more stable proteins that synthesize and destroy them. The

following neuronal systems lent themselves to mapping through enzyme localization: the cholinergic system through choline acetyltransferase, the GABA system through GABA transaminase, and the glutamate system through phosphate-activated glutaminase. While developing the methodology for GABA transaminase, we stumbled upon neurons positive for NADPH diaphorase, later shown to be nitric oxide synthase, and these were also mapped.

The Cholinergic System of Brain

In the days before central neurotransmitters were established, the most promising candidate was acetylcholine. However, the definition of cholinergic cells in brain lagged far behind that of other neurotransmitters such as the catecholamines, serotonin, and GABA. Loewi, with his elegantly simple 1921 experiment of setting up two frog hearts in series, had, as Sir Henry Dale described, 'rung up the curtain on neurotransmission.' Loewi stimulated the vagus nerve of the first heart and allowed the perfusing solution to be dripped upon the second heart from which the vagus nerve had been cut. The second heart slowed, and the material, first named 'Vagusstoff,' was identified in 1926 as acetylcholine. Quastel and associates in 1936 incubated brain slices with glucose and oxygen in the presence of eserine. They obtained a material indistinguishable from acetylcholine by bioassay. De Robertis and colleagues in Argentina, and Whittaker and his team in England, developed the technique of differential centrifugation and were able to identify a fraction containing pinched-off nerve endings that they called synaptosomes. They found that choline acetyltransferase, the enzyme that synthesizes acetylcholine, occurred in the synaptosomal fraction. Distribution studies showed a highly unequal distribution in brain, indicating the likelihood of specific pathways using acetylcholine as the neurotransmitter.

The method of localizing a neurotransmitter synthetic enzyme by immunohistochemistry had been pioneered by Eugene Roberts and colleagues. They had established GABA as a neurotransmitter by purifying glutamic acid decarboxylase, developing antibodies to it, and using the technique of immunohistochemistry to localize its presence in specific pathways.

The group from our laboratory that applied this approach to the cholinergic system was an unlikely team. Vijendra Singh, who had come from India to take his Ph.D. under Shan Ching Sung in our laboratory, took on the job of purifying choline acetyltransferase as his first postdoctoral project. His efforts were crowned with the first purification of the enzyme. He innoculated a rabbit with the protein and obtained the first antibodies to it. By today's techniques, the antibody titer in the serum would have been sufficiently high to do the job of brain mapping, but in the early days

of immunohistochemistry the techniques were too insensitive. A second biochemist, this time from Taiwan, carried on Vijendra's work, scaling up the purification and producing higher titers of rabbit antibodies. Frank (his adopted English name) Peng was a slight, intense young scientist who spoke English with such a heavy accent that everyone had difficulty understanding him. We were next joined by Hiroshi Kimura, a young and highly skilled morphologist from Kyoto, Japan. Hiro had a mild hearing deficit from the chloromycetin he had been given for a serious ear infection. He too spoke English with an accent, but it was completely different from Frank's. Between accents and hearing difficulties, communication between these two was well-nigh impossible. Kimura was certain that Peng could not make sensitive antibodies. Peng was certain that Kimura did not understand how to use them. We did the language translation and stressed the rewards of team efforts. In the end, they had the perfect combination of skills, and the cholinergic system of brain was completely mapped.

Given the importance of acetylcholine as a peripheral neurotransmitter, we had expected to find more cholinergic groups than were present. Striatal interneurons were anticipated from our previous lesion studies, as were cranial nerve nuclei due to their analogy with anterior horn cells. However, the basal forebrain cholinergic system was a surprise, as was the group in the pedunculopontine area.

Nitric Oxide Neurons

The discovery of nitric oxide neurons in the CNS happened in a most curious way. Steve Vincent, doing his Ph.D. work under Edie's supervision, developed a pharmacohistochemical method for GABA transaminase (GABA-T), by analogy to the then known pharmacohistochemical method for acetylcholinesterase. The purpose was to use this GABA-T method as a way of mapping putative GABAergic neurons. He asked Uschi Scherer-Singler, a technician in the laboratory, to prepare one of the reagents. On his next experiment, he was amazed to see beautiful Golgi-like staining of a subset of neurons that did not have the morphology or expected distribution of GABAergic neurons. Displaying the excellent scientific talent that he would subsequently demonstrate in many ways, he named the neurons 'magic neurons' and pursued the question of why they were histochemically stained. He found that Uschi had mistakenly used malic acid rather than maleic acid in the key buffer. He and Hiro Kimura soon determined that the staining was revealing NADPH diaphorase. Another Japanese colleague, Kimi Mizukawa. worked with Steve in our laboratory to map the NADPH diasphorase-positive neurons in the cat brain. Steve later joined our faculty, and one of his graduate students, Bruce Hope, showed NADPH diaphorase to be neuronal nitric oxide synthase.

Mapping of GABA Neurons by GABA Transaminase

Eugene Roberts and coworkers eliminated any last doubts about GABA being a neurotransmitter when they identified neurons and nerve endings containing its synthetic enzyme glutamic acid decarboxylase (GAD). The immunohistochemical methodology they employed was sensitive enough to reveal certain groups of neurons, but it was not a practical way to do a complete mapping of the brain. We wished to develop a simple method for doing so and thus developed the pharmacohistochemical method for GABA-T. GABA-T, being a transaminase, would react with formazan dyes to yield visible products, but its localization was not restricted to neurons. Astrocytes, being responsible for picking up neuronally released GABA, contained large quantities. Steve Vincent and Hiro Kimura overcame this problem by applying a strategy previously developed by Larry Butcher for acetylcholinesterase. An irreversible GABA-T inhibitor was given to a rat *in vivo*. Sacrifice was then timed so that recovery of GABA-T would occur in neurons but not in the less active glial cells. Ethanolamine-*O*-sulfate was used as the specific and irreversible inhibitor of GABA-T. Toshi Nagai and Masa Araki, two of Hiro Kimura's successors from Japan, then applied the technique to the first complete mapping of GABA neurons, i.e., those containing high levels of GABA-T. Many of the neurons were types already known to be interneurons, but others were associated with key pathways, particularly in the basal ganglia.

Glutamate Pathways

Physiologists had long been aware that glutamate and aspartate are strongly excitatory, and it was suspected that they played major roles as excitatory neurotransmitters in brain. However, proving this suspicion and localizing them to specific pathways was difficult because they are amino acids with numerous nontransmitter roles. Glutamate, for example, is incorporated into proteins and peptides, is involved in fatty acid synthesis, and contributes to the regulation of ammonia and the control of osmotic or anionic balance. It serves as a precursor for GABA and for various Krebs cycle intermediates, and it is a constituent of important cofactors such as glutathione and folic acid. How then could neurotransmitter glutamate be distinguished? Our first attempt was to use high-affinity, sodium-dependent uptake in synaptosomal fractions from key areas as a possible measure of glutamatergic nerve endings. Spencer had suggested that the massive corticostriatal path used glutamate on the grounds that excitation of striatal cells by stimulation of this pathway was antagonized by diethyl glutamate. Working with Uschi Scherer and Vijendra Singh, we found that surgical lesions of the corticostriatal path in rats caused a significant 40% reduction in glutamate uptake in the synaptosomal

fraction of the striatum. Thalectomy had no such effect, and indexes of other neurotransmitter systems, such as choline acetyltransferase or GAD activity, were not affected. When we published our results 1977, this was the first chemical evidence supporting a neurotransmitter role for glutamate in a defined tract.

Subsequently, Haru Akiyama in our lab, working with Dr. Kaneko of Kyoto University, used an immunohistochemical method for phosphate-activated glutaminase (PAG) to stain neurons in the human cerebral cortex. Staining was seen in pyramidal neurons, believed to be glutamatergic, but also in the large basket cells believed to be GABAergic. Thus, PAG appears to play a role in generating both transmitter glutamate and glutamate as a precursor for GABA. There was a drastic depletion of PAG-positive pyramidal neurons in the cortex in cases of Alzheimer's disease, a depletion that could also be found by biochemical assays of PAG in tissue homogenates. Working with Akiyama and Hisaki Kamo, another colleague from Japan, we eventually used such biochemical assays to show a highly significant correlation between the PAG losses in various regions of Alzheimer cortex measured postmortem and the decreases in glucose metabolism measured premortem by positron emission tomography.

In the second edition of *Molecular Neurobiology of the Mammalian Brain*, published in 1987, 9 years after the first edition, the only candidate added to the confirmed list of neurotransmitters was histamine. 'The Promising Peptides' had become 'The Prominent Peptides' with apparent functions as cotransmitters. As of this writing, no new, nonpeptide neurotransmitters have been found. The list is incomplete since there are established anatomic pathways in brain that are not served by any of the known neurotransmitters. Important discoveries are yet to come.

Biochemical Pathology and the Effects of Aging

To provide a link with human disease, we applied the radioactive techniques we had developed for the synthetic enzymes [i.e., tyrosine hydroxylase, choline acetyltransferase (ChAT), and GAD] to a study of human postmortem brains from cases dying without neurological disease as well as cases suffering from a variety of neurological disorders. It was a frustrating time because applications for support were repeatedly turned down on the grounds that it would be impossible to obtain useful enzyme data on postmortem brains. We did the work anyway, with Pat doing all the dissections and Edie all the chemistry. When we finally submitted our initial survey to the *Journal of Neurochemistry*, Pat wrote in the acknowledgment 'This research was not supported by the Medical Research Council of Canada.' The editor wisely insisted this 'acknowledgment' be deleted.

Analysis of the voluminous data was a challenge in those pre-home computer days: It involved learning Fortran, writing a suitable program, having a few thousand punch cards prepared, and, finally, feeding them through the university's mainframe computer—better than the old-fashioned calculator of our earliest years but rather different than the ease of such analysis on a modern Macintosh computer.

One of the unanticipated outcomes was a substantial decline in the regional level of many of these enzymes with age. This was particularly true of tyrosine hydroxylase in the striatum. The results were treated with skepticism since the younger cases were accident victims, whereas the older cases died from various fatal illnesses. Therefore, Lucien Cote and Stanley Fahn repeated the study using only people dying of knife or gun shot wounds to the heart—needless to say, they worked in New York City. Their curve was almost identical to that which we reported.

We also found declines in cortical choline acetyltransferase. Were these declines due to losses of the cell bodies of origin, or did they merely represent less dynamic enzyme synthesis? To answer this question, we did cell counts of dopaminergic nigral neurons and cholinergic basal forebrain neurons in patients dying at various ages. In both cases, cell counts decreased to almost half by age 65–75. Therefore, the decline was largely accounted for by cell loss. It is still not understood why there is such selective neuronal loss with aging, but it is not restricted to humans. Similar decreases in aged rodents and other species have been recorded.

One of the exciting findings in our biochemical studies on postmortem brains was the dramatic decline in glutamic acid decarboxylase and choline acetyltransferase, but not tyrosine hydroxylase, in the striatum of Huntington's disease cases. This was evidence of GABAergic and cholinergic cell loss in the striatum, with no loss of dopamine nerve endings. Was there some way this could be duplicated in an animal model? The idea of how this might be done came from following up on the excitotoxic discovery of John Olney.

Excitotoxicity

John Olney's discovery of excitotoxicity opened the door for many branches in neuroscience. Excitotoxic agents are now used to define anatomical pathways and to create animal models of disease. The excitotoxic phenomenon has also generated theories regarding the causation of such diverse neurological diseases as Huntington's disease, epilepsy, Alzheimer's disease, amyotrophic lateral sclerosis, Parkinson's disease, and, in Olney's continuing work, developmental abnormalities. Glutamate is the most ubiquitous neurotransmitter in brain, and almost all neurons have large numbers of glutamate receptors on their surface. Therefore, neurons

exposed to overexcitation of these receptors will become irreversibly depolarized, leading to their rapid demise. None of this was understood at the time Olney commenced his seminal experiments. He followed up on the finding of Lucas and Newhouse in 1957 that retinal neurons degenerated following parenteral administration of glutamate to infant mice. He confirmed these findings and also discovered that such administration caused degeneration of CNS neurons, particularly in the circumventricular organs not protected by the blood–brain barrier. Olney also tested a series of glutamate analogs and found that they duplicated the effects of glutamate. Kainic acid was particularly powerful, being much more toxic than glutamate.

John and Pat had made presentations at the same symposium of the American Neurochemical Society in New Orleans. The broader significance of Olney's discovery escaped Pat but not Edie. When she read John's Neuroscience Society abstract, she reasoned that kainic acid might reproduce the axon-sparing lesion of Huntington's disease if injected directly into the striatum. She ordered kainic acid from the lone supplier, Sigma Chemical of St. Louis. None was available. We subsequently learned that, due to the modest price, Olney had ordered 5 grams, inadvertently cornering the world's supply. Eventually, some kainic acid arrived, and experiments injecting it into the striatum of mature rats commenced. The results were dramatic. Local neurons were destroyed, but nerve endings and axons of passage were spared. Edie vividly recalls meeting Pat at the airport when he returned at about 1 AM from a trip and saying breathlessly, 'We have a model of Huntington's disease.' Our spirits continued to be high during the subsequent few weeks while we verified the 'model,' tested the neurochemical effects of kainic acid injections into the substantia nigra, and prepared a brief paper. Unbeknownst to us, Joe Coyle and Robert Schwarz were doing similar work at Johns Hopkins University. Our findings were published in *Nature* 1 week after the paper by Coyle and Schwarz appeared.

Ted Evarts, on the program committee of the Society for Neuroscience, invited Pat to give the public lecture at the 1976 neuroscience meeting in Toronto. That lecture, 'Mood and Movement—Twin Galaxies of the Inner Universe,' described the biochemical neuroanatomy that resulted in antipsychotic agents inducing extrapyramidal disorders. The new model of Huntington's disease was an important feature of that lecture.

We soon learned that the massive corticostriatal glutamate pathway was essential to the kainic acid effect. Lesioning the pathway reduced the excitotoxicity of kainic acid by 100-fold! The potential of this new technique seemed enormous. Electrolytic lesioning of the brain, the method previously used to establish neuroanatomical pathways and to learn the function of various groups of neurons, severed axons of passage. The results were always suspect. Here was a way of targeting only the

neuronal population selected for study and allowing, for the first time, clean results to be obtained.

In order to provide an easy source of information to the neuroscience community, we teamed up with John Olney to edit a monograph *Kainic Acid as a Tool in Neurobiology* to be ready for the 1978 neuroscience meeting. We invited Dr. T. Takemoto of Tokushima Bunri University to write a chapter for this monograph. He was astonished by the request but delighted that his work should prove of broad interest. His chapter was written in Japanese. Dr. Toshi Hattori, then a colleague in our laboratory, translated it into 'Japanese English,' and Edie turned it into American English. The effort proved worthwhile because the chapter was fascinating. Dr. Takemoto had isolated kainic acid from the Japanese seaweed *D. simplex* and named it 'the demon from the sea.' It had been used for generations as a method of killing intestinal worms. He followed up by investigating another algae, *Chondria armata*, that had also been used to kill intestinal worms but only in some of the remote provinces of Japan. The active material turned out to be domoic acid. He then turned to a fly-killing mushroom called *Ibotegutake* and isolated ibotenic acid and finally to the seeds of a green creeping vine found in North Vietnam and the Kwong-chow province of China to isolate and identify quisqualic acid. All these compounds were found to be effective in killing swine ascaris, presumably because of their excitotoxic properties. These had been noted by Shinozaki of Tokyo, who also contributed to the volume. While we were working on the kainic acid monograph, Shan Ching Sung of the Kinsmen Laboratory told us that, when he was growing up in Taiwan during World War II, he and all the other schoolchildren had to drink an extract of seaweed every year to combat intestinal worms.

Neuroinflammation and Alzheimer's Disease

Our studies on biochemical pathology took an unexpected turn in the 1980s. We were led away from neurons and neurotransmitters and into a study of glia. We entered a realm of neuroscience we never dreamed existed. That is, the capacity of brain to mount its own innate immune response when challenged and the resultant autotoxic effects on neurons when this response exceeds a threshold of tolerance. The phenomenon is now commonly referred to as neuroinflammation, and it plays a role in all chronic degenerative neurological diseases.

This new direction commenced in the early 1980s when a determined woman marched into our laboratory saying 'You people study the brain, why don't you do something useful?' Phyllis Forsythe was a doughty lady whose husband developed Alzheimer's disease in his forties. She was of modest means but strong determination. She had been unable to find medical help or community support of any kind for her husband's problem.

She gathered some friends together who were in similarly tragic circumstances and they formed a tiny society that they named The Alzheimer's Support Association. We were quite moved by this entreaty and decided she had a strong point about the direction of our laboratory. Pat asked his colleague in the Provincial Government, the Honorable James Nielson, who was Minister of Health, what his ministry might do about the clinical problem. Being a highly compassionate politician, he immediately made funds available to establish an Alzheimer Disease Clinic at the University of British Columbia. It was the first such clinic in western Canada. Phyllis Forsythe's organization evolved into the Alzheimer Society of British Columbia, which now offers support services throughout the province and is affiliated with the national association in Canada.

The question we pondered was how best to investigate the disease. There were some starting points. Peter Davies and colleagues had found the first enzymatic defect, a reduction of cortical choline acetyltransferase. Peter Whitehouse and colleagues had identified this as being due to loss of basal forebrain neurons. Having mapped the cholinergic system of brain, we were familiar with its localization. However, pursuit of this did not seem to be a productive long-term goal since it was mainly pyramidal neurons that developed neurofibrillary tangles. At the time, there were suspicions that Alzheimer's disease might be of viral origin and, more specifically, due to a herpes infection. Herpesvirus was known to live in neurons, especially those of the trigeminal ganglia, and access to the brain could easily occur through the olfactory system, spreading to the rhinencephalon. We collected Alzheimer cases and started a collaboration with Donald McLean, our UBC virologist, and his assistant Kathy Wong. They had recently obtained beautiful EM pictures of the AIDS virus from biopsy tissue and submitted a report to *Lancet*. Unfortunately for them, the reviewers did not believe the data, and the manuscript was rejected. Another group was more fortunate. They submitted almost identical pictures a year later that were published as the first observation in human AIDS cases.

Our collaboration was producing no positive evidence of herpes particles. Could some other virus be responsible and, if so, how should we look for it? Local immunologists suggested hunting for indirect evidence, such as expression of HLA-DR. What was HLA-DR? We were given a briefing. This was an antigen, prominently expressed on immunocompetent cells, that should be present if any form of infection existed. Meanwhile, Joe Rogers of Sun City, Arizona, was pursuing the same hypothesis of herpes infection being the cause of Alzheimer's disease. He too was looking at HLA-DR as a possible method of gaining indirect evidence of a viral infection. He presented his data at the 1986 neuroscience meeting in Washington, DC. His abstract preceded our publication of HLA-DR expression in Alzheimer brain. Our own immunohistochemical work was

conducted by Shigeru Itagaki, another of Hiro Kimura's students. He applied a modification of the standard diaminobenzidine immunohistochemical procedure that had been brought to our laboratory from Japan by Hisao Tago. This nickel ammonium sulfate modification improved sensitivity by more than 100-fold, producing a highly visible dark blue stain. We could hardly believe our eyes when we first looked at Shigeru's slides. Here were intensely stained cells prominently associated with senile plaques of a kind we had never before seen. We turned to our mentor Bill Gibson, who had worked with del Rio Hortega, and asked him if these could be microglia. He sent us his copy of Hortega's original 1919 publication. In it were Hortega's drawing of cells that were identical to the ones we observed. We submitted our findings only to have the paper rejected. Everyone 'knew' that HLA-DR was expressed only on immunocompetent cells and that microglia were of epithelial origin, of still unknown function, but certainly not immunocompetent! We finally managed to get a paper accepted by *Neuroscience Letters* but could not find a published paper by Joe Rogers.

Tuck Finch was organizing an Alzheimer meeting with Peter Davies that spring in Cold Spring Harbor, New York. Tuck invited Pat, saying it was about time people heard something different about Alzheimer's disease. He also invited Joe Rogers for the same reason. Pat and Joe met at Cold Spring Harbor, where they presented almost identical results. When Pat asked Joe why he had not published his findings, Joe said he kept being turned down by referees. They immediately became fast friends. Two were stronger than one.

We immediately began searching for activated microglia expressing HLA-DR in a variety of other neurological conditions. In all neurodegenerative diseases examined, most of which were clearly noninfective, such activated microglia could be found in association with the lesions. Obviously, this was a more general phenomenon and not one restricted to infectious diseases.

About this time Alzheimer researchers at Athena Neurosciences had become interested in the subject and invited Pat to a private meeting at their laboratory. Also invited was Neil Cooper, an expert on complement. Neil said that if an infection were present, complement would be activated. 'How do you investigate for that?' Pat asked. Neil explained the basics of complement activation. Neil advised us to look for the presence of C3d and C4d since these were amplified fragments of activated complement covalently attached to target tissue. We obtained appropriate antibodies and were once more rewarded with dramatic staining of Alzheimer lesions. Only later did we find that Piet Eikelenboon of The Netherlands and Ishii and Haga of Japan had found the opsonizing components of complement attached to senile plaques almost 7 years before. We also looked for the membrane attack complex of complement and, to our astonishment, found

it richly expressed on damaged neurites. Here was the smoking gun of autodestructive damage!

Joe Rogers is a warm-weather guy well suited for the Arizona climate. However, there are limits, and Joe and his delightful family arrange minisabbaticals during the hottest months. And so Joe came to join us in the summer of 1990. In between rounds of golf, we spent hours hunting through sections attempting to find evidence of immunoglobulin antibodies that would be responsible for complement activation. There was no convincing evidence. The following summer, Joe joined Neil Cooper at the Scripps Institute, where they explored whether complement could be activated without antibodies. They made a seminal discovery, namely, that beta-amyloid protein was a complement activator. Here, then, was an explanation of the finding of complement activation in Alzheimer brain. However, where did the complement come from? The common belief was that liver must be the source, but if this were true, how did complement reach the brain? Several laboratories began examining this question, including ours, Joe Rogers' in Sun City, Yong Shen's at Abbott Laboratories in Chicago, and Tuck Finch's in Los Angeles. The Finch group first developed evidence of neuronal production, Doug Walker of our team found evidence in microglia and astrocytes, and Scott Barnum's group found evidence in astrocytes. Yong Shen's group also found evidence in cultured neurons. In summary, many brain cell types were found to be complement producers. Thus, evidence was slowly accumulated showing that complement was produced locally in brain, upregulated and activated in Alzheimer's disease, resulting in autoattack on neurons by the membrane attack complex.

Several laboratories now entered the hunt for the presence in brain of molecules known to be associated with inflammatory processes in the periphery. Inflammatory cytokines, acute phase reactants, proteases, protease inhibitors, and coagulation factors were all found to be present and synthesized locally in brain. Alzheimer's disease has turned out to be a textbook collection of these inflammatory molecules.

Zaven Khachaturian, then coordinator of the National Institutes of Health programs for Alzheimer's disease, convened a meeting in Bethesda in late 1989 to 'brainstorm' new approaches. Joe Rogers was a featured speaker and Pat was invited to discuss his paper. Joe and Pat had discussed over coffee how Alzheimer's disease might be treated if inflammation really were contributing to the pathology. Pat said, 'Old-time rheumatologists would have given aspirin.' In commenting on Joe's paper, Pat blurted out the comment, 'An aspirin a day keeps the gerontologist away.' It was greeted with roars of laughter. Zaven, in summarizing the meeting, warned that this outrageous idea should not be taken seriously. Returning home on the plane, Pat, in a somewhat chastened mood, considered that maybe people with rheumatoid arthritis might really be less

likely to have Alzheimer's disease than the general population. Pat made a request of Cyril Nair of Statistics Canada for separation data on patients diagnosed as having both rheumatoid arthritis and Alzheimer's disease. The numbers were unusually low. Calls to rheumatology clinics in Canadian cities turned up little information. Most rheumatologists said they had never seen a case of dementia. 'Why not?' Pat would ask. Most said they thought such patients must be going elsewhere for treatment. However, John Sibley of Saskatoon was operating a clinic at which rheumatoid arthritis patients had been closely monitored for many years. He was able to supply reliable data showing a remarkably low prevalence. Joe Rogers managed to obtain data from a large rheumatoid arthritic clinic in Arizona. The combined data showed a prevalence of Alzheimer's disease amongst subjects in rheumatoid arthritic clinics to be almost identical with those recorded in hospital separations. The data were submitted to *Lancet* and published in 1992. Anti-inflammatory drugs were suggested as one of four possible explanations for the data.

Months later, Zaven Khachaturian and Tuck Finch arranged a private meeting in San Diego to which many immunologists were invited to review our data and hypothesis. Stoney silence greeted our presentations. Afterwards, it was sagely agreed that the epidemiological information was the result of a 'flawed study.' Fortunately for us, others were not so sure the data should be dismissed. Now there are more than 20 published epidemiological studies indicating that patients known to be taking anti-inflammatory drugs, or having conditions for which such drugs are routinely used, have a substantially lower prevalence of Alzheimer's disease than the general population.

Joe followed up the epidemiological data with a small, double-blind, 6-month trial of indomethacin in Alzheimer's disease. It appeared to arrest progression of the disease. However, attempts to treat Alzheimer patients with low-dose corticosteroids failed, and so the true effectiveness of anti-inflammatory therapy in Alzheimer's disease must await future studies.

Joe and his family returned to Vancouver for two more summers of highly productive collaboration. His arrival on one of these occasions preceded that of his family. It turned out he had first come to compete for a spot from the Northwest in the National Seniors PGA Golf Championship. It was played in Seattle, but Joe failed to qualify. He announced when he arrived in Vancouver that this would be a particularly productive summer because he was giving up the game of golf—his astigmatism made it impossible to line up putts with accuracy.

About 2 weeks later, Pat received a call from Joe. 'Where is Kelowna?' he asked. I explained it was on B.C.'s Lake Okanagan. His family would love a weekend in that beautiful resort town. On Monday morning, Pat noticed a tiny item on the sports page of the *Vancouver Sun* newspaper: J. Rogers from Arizona had won the Okanagan Invitational Golf Tournament!

Much of our work on inflammatory markers in postmortem tissue from Alzheimer's disease and other degenerative neurological diseases was carried out by a succession of highly competent and imaginative students of Hiro Kimura. After returning to Japan from our laboratory, Hiro took up a post at Shiga Medical School, then a newly formed National University in Japan. He became head of their neuroanatomy program, and his students began to arrive in our laboratory for postdoctoral work. Hisao Tago, Shigeru Itagaki, Haru Akiyama, Ikuo Tooyama, Tatsuo Yamada, Toshio Kawamata, Akinori Matsuo, and Kazuo Terai proved to be wonderful and dedicated colleagues who did masterful work. During this same period, Kazuo Shigematsu, also from Japan, modeled lesions in rat brain that produced accumulations of amyloid precursor protein and activation of microglia.

In 1990, Hiro Kimura asked whether we would like to reverse the trend and come to Shiga to work in his institute for a year. It sounded like an excellent idea. Therefore, Pat became the first visiting professor from North America at Shiga University and Edie accompanied him. Hiro arranged a small apartment in the village of Ohtsu, a short drive from the medical school. Due to commitments in our own laboratory, it was not possible for us to remain continuously at Shiga, but it was relatively easy to commute so we spent the year bouncing back and forth between Vancouver and Shiga. It sounds like a long way, but with direct jet travel, it is little more than a trip across the continent.

Life in Japan was a delight. Our Japanese was hopeless, but everyone at the lab spoke English fluently and people everywhere seemed to understand a little English. The village was full of attractive Japanese restaurants, and there was a McDonald's if reversion to North American food seemed required. The supermarket was filled with a rich variety of items so home cooking was also easy. We did make mistakes in purchasing packaged foods, and our miscues were always greeted with merriment when we brought the unidentified packages into the lab the next day.

A particular pleasure was watching Japanese children on their way to school in the early morning. They were all neatly decked out in school uniforms, including caps of different colors for each of the schools. They assembled in groups on corners. When all members of a group had arrived at a particular assembly point, they all headed off to the school yard together, with the older children shepherding the younger ones.

At a university reception after one of Pat's evening lectures, one of the psychiatrists told us that leprosy patients never got dementia. We were skeptical. He insisted because he regularly visited one of the main leprosy hospitals on the island of Nagashima, not far from the city of Okayama. Patients were closely followed and dementia would have been easy to spot. The psychiatrist explained that the leprosy patients were not allowed to leave the island, were not allowed to have children, and lived in separate

homes in the community. It was self-reliance that protected them, he said, since they had no families to look after them in their senior years. 'No,' we explained, 'Alzheimer's disease is an active, malevolent disorder and cannot be prevented by self-reliance.' However, the story of lack of dementia was so compelling that Hiro, Edie, and Pat arranged a visit to the island. They were shown around by Dr. Nobuo Harada, a cultured and courteous gentleman. He had introduced dapsone for the treatment of leprosy in Japan in the late 1940s. The death rate immediately decreased and so did the prevalence of leprosy. Most of the people in the colony were now over 65 years old. They lived in separate cottages and were followed weekly in the hospital clinic. There is no way that developing dementia could be missed. Could dapsone be responsible? We rushed back to the library in Shiga and began to look up all the papers we could find on the properties of dapsone. To our astonishment, we found there were many reports indicating its anti-inflammatory properties. It had therapeutic value in such conditions as dermatitis herpetiformis, temporal arteritis, rheumatoid arthritis, and other disorders with known inflammatory features. We then went back to Dr. Harada and asked if it would be possible to survey other leprosy hospitals in Japan to determine the prevalence of dementia among those on and off dapsone.

The data were obtained in a few months. It turned out that leprosy cases over age 65 who had been maintained continuously on dapsone or its close relative promin had a prevalence of 2.9%. Those who had been taken off dapsone or promin within the past 5 years had a prevalence of 4.8%, whereas those who had been deemed to be cured and had been off dapsone or promin for more than 5 years had a prevalence of 6.25%, almost identical with the reported value for the Japanese population in general. These data imply that dapsone should be a useful preventative or treatment for Alzheimer's disease, but so far clinical trials to test this have not been undertaken.

At the time of this writing, the phenomenon of endogenous immune reactions in brain is being actively explored in our laboratory as well as in many others throughout the world. It cannot be predicted what developments will take place. In the early stages of this exploration, experiments were concentrated on determining if observations on peripheral inflammatory conditions applied to brain. Now the reverse is beginning to take place, and a search is under way to determine whether the molecules that support the hypothetical autotoxic loop in Alzheimer brain are also present in local tissue in conditions such as heart disease, atherosclerosis, and rheumatoid arthritis.

Brain is partially isolated by the blood–brain barrier, a situation that inspired investigation as to whether inflammatory molecules previously believed to be produced in liver or peripheral immune organs were produced in brain. The fact that neurons, astrocytes, and microglia could

produce such molecules as the complement proteins and their inhibitors has inspired a reevaluation of many peripheral conditions to determine whether local inflammatory processes are responsible for much of their pathology. The narrow view that self-destruction of tissue is caused only by autoimmune attack of the adaptive immune system needs to be broadened. Investigation of the neuroinflammatory component of Alzheimer's disease has taught us that innate immunity and local tissue reactions may be key factors in a broad spectrum of human diseases.

A Political Sideline

Our activities have not been entirely confined to neuroscience, although neuroscience has always played a leading role. The Society for Neuroscience is acutely aware of the role politics plays in its affairs. Pat spent a quarter of a century in the hurly-burly of B.C. politics.

The British scientist–politician–philosopher C. P. Snow wrote a penetrating article years ago about the huge gulf that exists between science and politics. He named them 'The Two Solitudes.' And so they are. In politics what counts is image. In science what counts is substance. Pat had a taste of both as a member of our British Columbia Legislature from 1962 until 1986 and as a Minister of the Crown from 1975 until 1986. He led a double life, each with its separate rewards. Tenure in politics is usually brief, and Pat always regarded it as a temporary interlude, having mixed feelings about getting reelected and taking care to remain active in science. People of many backgrounds are motivated to enter politics as a means of furthering their interests. Science and technology are not popular motivations. As a consequence, the level of sophistication in high government circles about science and technology is regrettably low. This applies to all Western democracies, including the United States. Neuroscientists of today should do all they can to remedy that situation.

In Pat's case, the opportunity to enter politics was inherited from a famous uncle, Gerry McGeer. Uncle Gerry had been a member of the Provincial Legislative assembly, a mayor of Vancouver, a member of the Canadian House of Commons, and a member of the Canadian Senate. Pat was approached by liberal functionaries, asking if he would stand for the Legislative Assembly of British Columbia. Since that body met for only about 8 weeks a year in the winter, it seemed possible to combine it with scientific activities at UBC, especially since Edie would be in the lab to keep him posted. Pat agreed to run, but there were reservations about his background. The political professionals recommended that Pat lean hard on the ghost of Gerry McGeer, 'and just keep the university stuff out of it.' At one meeting, a particularly persistent lady was determined to ferret out the truth: 'Is it true you are a professor at the university?' she demanded.

Pat confessed. 'Do you do research on the brain and behavior?' 'Yes,' he mumbled. 'Young man, I just want to know one thing. Are you going into politics out of any serious purpose? Or it is just professional curiosity?' Such skepticism was not novel.

Robert Louis Stevenson, in his early journalistic days covering the British House of Commons, remarked that it was the only insane asylum run by the inmates. Debates are not peer reviewed. When the legendary C. D. Howe, a senior minister in the Canadian government, was pushing to build the Trans Canada Pipeline, a colleague told him there would be a debate in the Canadian House of Commons. 'A debate,' snapped Howe, 'surely this won't degenerate into a debate.'

Throughout his political years, Pat remained active in neuroscience, but it took a lot of juggling, a lot of time, and a lot of patience on the part of his wife, who kept things going at the lab by day and informed him of its doings on nights and weekends. During the 1960s, there was still quite a lot of time for science, as Pat was a liberal opposition member and only had to take leaves of absence from the university to attend the legislative session each winter. Pat also made presentations at each neuroscience meeting since these were conveniently held in the fall. In September 1969, Pat visited the California legislature in Sacramento. Governor Ronald Reagan discussed with Pat the problem of student violence on U.S. campuses, especially in California, where there had been 18 deaths. The governor then invited Pat to address the California Senate. Pat informed the assembly that in Canada senators were appointed for life. There were cheers. Then he pushed his luck by saying he was in favor of elected senators. There were boos.

During this period, the government of British Columbia was led by the flamboyant, and now legendary, Premier W. A. C. (Wacky) Bennett. He was defeated in 1972 by the New Democratic Party (NDP) led by David Barrett, a social worker. The economy of British Columbia went into a precipitous decline under Barrett's socialist government, and demands for a united opposition rapidly escalated. After some uncertainty as to what form this opposition would take, Pat and two other liberal colleagues joined a remade Social Credit party elected in 1975 under the leadership of William Bennett, son of the former premier.

Pat, then one of the most experienced members of the Legislative Assembly, was called upon to assume many responsibilities with the new government. These cut seriously into the time he had available for science, but the premier was understanding about his double life so neuroscience carried on. Pat frequently took chapters intended for the first edition of *Molecular Neurobiology* . . . to cabinet meetings so that he could work on them during dull moments. The premier even understood that and said 'Don't worry Pat, I'll let you know when anything comes up that affects you.'

The NDP had started a compulsory automobile insurance company known as the Insurance Corporation of British Columbia, which immediately became Canada's largest insurance company. To gain political favor, the NDP had set automobile premiums at a ridiculously low level. Pat became the reluctant president and chairman of the board, in addition to his duties as minister of education and science. On the day in December 1975 when Pat assumed his new duties, the corporation ran out of money and had to borrow from the bank. The scientific solution to the problem was easy—double the premiums to make income equal outgo. The political solution was not so easy. Petitions protesting the increases were signed by hundreds of thousands of disgruntled car owners.

That spring, the American Society for Neurochemistry held its annual meeting in Vancouver. We were in charge of the local organizing committee. The arriving delegates were amused to see bumper stickers on taxi cabs and private automobiles everywhere that said 'Stick it in your ear, McGeer.' Pat survived the protest but not without sacrificing a good deal of popularity.

Premier Bennett, understanding the opportunity to take advantage of Pat's scientific background, placed him in charge of promoting science and encouraging scientific industry. Politicians can develop policy but must rely on others for administration. Policies, therefore, can be no better than the ability of others to make them work. With respect to scientific policies, this is a significant problem for all governments. For example, Pat instituted a program of grants to be given to academic and industrial scientists, but there was no way government could administer them. He had to create a British Columbia Science Council of volunteer professionals to make the program work.

Over the years in government, Pat oversaw the development of an Open Learning Institute for satellite education in the remote parts of British Columbia as well as the formation of 11 new institutes and colleges. He encouraged the foundation of industrial parks at the major universities and the development of industry-liaison offices within the universities. Such offices have been one of the most lasting successes of all his initiatives. Pat also had portfolios for communication and, in his last year in 1986, international trade. He was responsible for the British Columbia Pavilion and official visitors to British Columbia in the world's fair of EXPO '86. These were busy times, but Pat kept up his scientific work. Edie kept him briefed on both the literature and the laboratory, and the postdocs adjusted to strange hours. Pat would meet with them in the evenings as well as on weekends. He managed to contribute to 150 papers during that period as well as cowrite both editions of *Molecular Neurobiology of the Mammalian Brain* with Sir John Eccles and Edie. He also attended the annual meeting of the Society for Neuroscience in each of those years, and in three of them he was a traveling Grass lecturer.

Pat and Edie got to meet with most of the political leaders throughout the world during those days. There were many formal and informal visits to British Columbia, especially during EXPO '86. The educational institutions and many of the programs that Pat instituted have survived, but the science portfolio was eliminated as soon as he left. Science was too low a priority. Pat likes to say 'I was the first minister of science British Columbia ever had. I was also the last minister of science British Columbia ever had.' In comparing politicians and scientists, Pat believes that politicians are ordinary people in extraordinary circumstances; scientists are extraordinary people in ordinary circumstances.

Killer Whales

What do *Orcinus orca* whales have to do with neuroscience? The answer in 1962 was the possibility of a very large and complex brain. At that time, these whales were regarded as the most dangerous marauders to roam the world. They had frequently been observed attacking sea lions and much larger sperm whales. Thus, they were named killer whales. Scott had reported in his Antarctic expedition that these whales attempted to tip the ice floes to tumble his men into the sea as prey. At the behest of British Columbia fishermen, the Canadian armed forces had mounted guns in Johnstone Strait to shoot at them as they traversed the inside passage. Marineland of the Pacific, which had successfully captured dolphins and larger pilot whales, attempted to catch a killer whale in American waters just south of Vancouver. They mounted a cannon on their boat in case of trouble. When they actually lassoed a whale, they thought it was attacking their boat and shot the poor beast. They returned to California, reinforcing the notion of killer whale ferocity.

Murray Newman, the highly creative director of the Vancouver Aquarium, wished to have a model of this denizen of the deep to display in the aquarium's newly renovated quarters. However, nobody could make a model since too little was known about the whale's size and shape. Murray conceived a plan to harpoon a killer whale as it passed a lighthouse on Saturna Island and then to model it before dispatching the remains. Pat asked Murray if he could examine the brain. Dolphins, the smaller relatives of killer whales, had large brains. Might this be the case for killer whales too. 'Sure' said Murray, 'but why not join the expedition?' Therefore, Pat became part of the team.

What happened next was totally bizarre and unexpected. A killer whale was harpooned as planned, but the harpoon passed right through soft tissue behind the head, creating a leash. The harpoon line was attached to the supply boat, and we debated what to do as the whale swam quietly behind the boat. It was decided to tow it to dry dock where the rope could be released and the animal given antibiotics. The whale was maintained

in dry dock and subsequently moved to a wired pen off Jericho beach in Vancouver. We were uncertain what to feed it because the diet of killer whales was unknown. It took some time for the whale to take up domestic feeding, but once it commenced eating fish, the whale responded very quickly, much as had previously been observed with dolphins. Unfortunately, the whale developed a lung infection and died. A model of that first whale adorns the Vancouver Aquarium foyer, but a more significant result was a scientific report on the detailed physiological and biochemical parameters of *O. orca*. The most striking organ was the brain. It weighed 6450 grams, one of the largest brain sizes ever recorded. The real value of the expedition lay in demolishing myths about killer whales.

The capture and domestication of that first killer whale led to a chain reaction of captures. Now, more than 32 aquariums throughout the world display these spectacular mammals. In each case, killer whales are the main attraction and chief source of revenue. Killer whales are no longer a feared and predatory species to be eliminated. They have delighted audiences throughout the world. They have become an admired and respected species to be carefully protected! Restrictions are placed on their capture, and there is now a flourishing environmental movement to free the whales.

Murray organized another whaling expedition in 1968. This was to the Canadian high Artic to observe the strangest of all cetaceans, the narwhal. The males have a protruding tusk, which is really a long, pointed upper incisor tooth. It is said that such whales inspired tales of the legendary unicorn. Pat was assigned the role of cook. The narwhals were observed in abundance along the northern coast of Baffin Island. Two years later, the team returned, this time netting five narwhals, which were flown back to the Vancouver Aquarium. Tragically, all five died, so narwhals are still a mysterious species, although their brain complexity cannot compare with that of killer whales.

Meetings

Young neuroscientists should take every opportunity to attend scientific meetings in their field. This is where inanimate names on scientific papers are transposed into personalities. It is where stimulating discussions on scientific problems can take place and shoulders can be rubbed with veterans in the field. Great distances often separate close scientific colleagues, and meetings provide the venue for future collaborations. The Society for Neuroscience meetings have become far too large for the intimacy we found so valuable in our early years in the field. We treasure memories of forming new friendships in the stimulating atmosphere of previously untraveled places. The early meetings of the International Society of

Neurochemistry gave us wonderful glimpses of such towns as Copenhagen (especially Tivoli), Wolfgang-am-Zee, Budapest, and Tokyo. After the meeting in Tokyo, we gave a talk at a Tokyo university on the basal ganglia. We were then taken out to dinner by the president of the university and some of the faculty members. Toshi Hattori, then in our laboratory and part of our group, whispered that it was the best Geisha house in Tokyo. As soon as we were seated, the head Geisha said something to our host, to which he replied very briefly. Toshi whispered to Edie, 'This will amuse you. She asked the president 'What is she doing here—a woman?' And the president said 'She's not a woman—she's a scientist."

The scientific meetings in the early days helped to overcome the feeling of isolation in neuroscience in Vancouver. However, we found that there were neuroscientists who felt even more isolated. We were taken on a bus tour to view the autumn leaves while attending a meeting in Quebec and Edie fell into conversation with the young man seated beside her. They exchanged first names and places of residence. He came from Boise, Idaho, and was complaining about how difficult it was to do neuroscience in isolation. Edie said she had the same problem. At which point he voiced one of the sincerest compliments we have ever received: 'Oh,' he said, 'but you're from Vancouver and the McGeers are there.' Everyone feels a little isolated in their own specialty, and meetings are a stimulating antidote.

Order of Canada

Canada is a country with diffidence toward honors. There is no such thing as a Canadian National Academy of Sciences. Prime Minister Mackenzie King issued a parliamentary order in the 1920s forbidding Canadian citizens to receive a British title, making Canada unique among British Commonwealth countries. Prime Minister Lester Pearson decided all of this was not quite right and so he established the Order of Canada in the 1960s. It has been inducting Canadian citizens prominent in the creative arts, sciences, and public service as companions, officers, and members for more than 30 years, but the Order, perhaps appropriately, is little known, even in Canada. Nevertheless, inductees are always proud to be recognized and are treated to a wonderful ceremony at Government House in Ottawa. We were nominated by a lady from eastern Canada who was completely unknown to us. That must have impressed the selection committee because we were accepted. She thought it would be appropriate for a husband and wife team to be jointly honored, and we were inducted together as officers of the Order of Canada in May 1995. Were we the first husband and wife team to be recognized? Yes and no. A husband and wife team, not from the scientific community, had previously been accepted, but before the ceremony was held they had a battle and divorced. They insisted that they be inducted in separate ceremonies.

Nonretirement

The University of British Columbia has mandatory retirement at age 65 but often provides space for faculty wishing to continue with their activities. Edie retired officially on January 1, 1989, and Pat on July 1, 1992. For us, retirement means we do all the things we did in the past except we do them as unpaid volunteers (and we are spared faculty department meetings!). Our lab continues to be international, with Claudia Schwab from Germany, Andis Klegeris from Latvia, and Koji Yasojima from Japan currently forming the main elements of our team. Claudia is an expert immunohistochemist; Andis is skilled at culturing microglia, neurons, and astrocytes; and Koji is a highly productive molecular biochemist. It is their skills that make it possible for us to continue producing new bits of novel scientific information—just as it was the help of many colleagues in the past who made our scientific careers productive. At this writing, we have contributed approximately 175 manuscripts since officially retiring and hope to contribute at least 200 more. There is so much unfolding in the world of neuroscience today that no other activity could hope to compete. Besides, the cause and cure of schizophrenia, Parkinson's disease, Alzheimer's disease, and a host of other disorders are as mysterious today as when we first entered neuroscience. The greatest excitement is still to come! However, we do envy the young neuroscientists of today who have such powerful techniques that they should be able to make rocket-like progress, whereas we were initially limited to a horse-and-buggy pace.

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