

Per Andersen • Mary Bartlett Bunge

Jan Bures • Jean Pierre G. Changeux

John E. Dowling • Oleh Hornykiewicz

Andrew F. Huxley • JacSue Kehoe

The History of Neuroscience in Autobiography

Edvard A. Kravitz

William Maxwell (Max) Cowan

James L. McGaugh • Randolph Menzel

Mircea Steriade • Richard F. Thompson

Volume 4

Edited by Larry R. Squire

EDITORIAL ADVISORY COMMITTEE

Marina Bentivoglio

Larry F. Cahill

Stanley Finger

Duane E. Haines

Louise H. Marshall

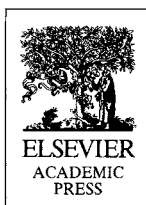
Thomas A. Woolsey

Larry R. Squire (Chairperson)

The History of Neuroscience in Autobiography

VOLUME 4

Edited by Larry R. Squire



Amsterdam Boston Heidelberg London New York Oxford
Paris San Diego San Francisco Singapore Sydney Tokyo

This book is printed on acid-free paper. ∞

Copyright ©2004 by The Society for Neuroscience

All Rights Reserved.

No part of this publication may be reproduced or transmitted in any form or by any means, electronic or mechanical, including photocopy, recording, or any information storage and retrieval system, without permission in writing from the publisher.

Permissions may be sought directly from Elsevier's Science & Technology Rights Department in Oxford, UK: phone: (+44) 1865 843830, fax: (+44) 1865 853333, e-mail: permissions@elsevier.com.uk. You may also complete your request on-line via the Elsevier homepage (<http://elsevier.com>), by selecting "Customer Support" and then "Obtaining Permissions."

Academic Press

An imprint of Elsevier

525 B Street, Suite 1900, San Diego, California 92101-4495, USA
<http://www.academicpress.com>

Academic Press

84 Theobald's Road, London WC1X 8RR, UK
<http://www.academicpress.com>

Library of Congress Catalog Card Number: 2003 111249

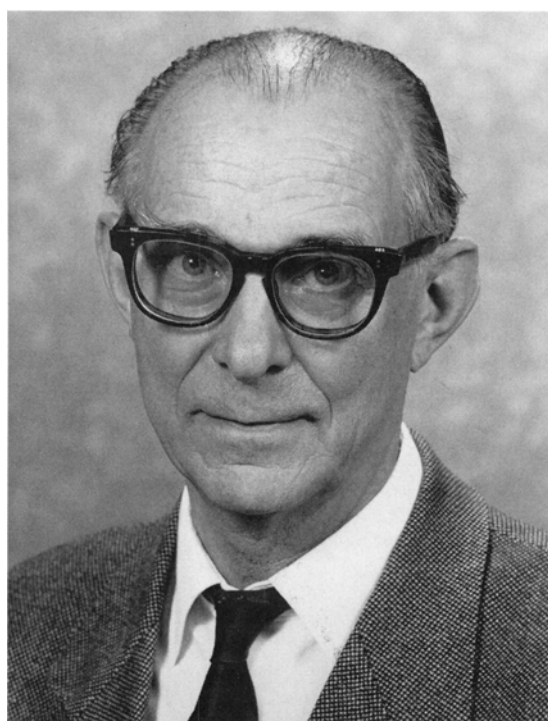
International Standard Book Number: 0-12-660246-8

PRINTED IN THE UNITED STATES OF AMERICA

04 05 06 07 08 9 8 7 6 5 4 3 2 1

Contents

| | |
|-----------------------------|-----|
| Per Andersen | 2 |
| Mary Bartlett Bunge | 40 |
| Jan Bures | 74 |
| Jean Pierre G. Changeux | 116 |
| William Maxwell (Max) Cowan | 144 |
| John E. Dowling | 210 |
| Oleh Hornykiewicz | 240 |
| Andrew F. Huxley | 282 |
| JacSue Kehoe | 320 |
| Edward A. Kravitz | 346 |
| James L. McGaugh | 410 |
| Randolf Menzel | 452 |
| Mircea Steriade | 486 |
| Richard F. Thompson | 520 |



Oleh Hornykiewicz

BORN:

Sykhiw (formerly Poland, now Ukraine)
November 17, 1926

EDUCATION:

University of Vienna, M.D. (1951)

APPOINTMENTS:

Department of Pharmacology, University of Vienna (1951)
Professor of Pharmacology, University of Toronto (1968)
Professor of Biochemical Pharmacology, University of
Vienna (1976)
Professor Emeritus, University of Toronto (1992)
Professor Emeritus, University of Vienna (1995)

HONORS AND AWARDS (SELECTED):

Höchst Foundation Award, University of Vienna (1965)
Gold Medal, Canadian Parkinson's Disease Association
(1970)
Gardner Foundation Award, Canada (1972)
Ludwig Schunk Prize, Justus Liebig University, Germany
(1974)
Wolf Prize, Israel (1979)
Lifetime Achievement Award, Clark Institute of
Psychiatry, Canada (1992)
Ludwig Wittgenstein Prize, Austria (1993)
Kardinal-Innitzer Prize, Austria (1997)
Billroth-Medaille, Gesellschaft der Ärzte in Wein,
Austria (2001)

Oleh Hornykiewicz is best known for his discovery of the dopamine deficit in the brain of patients with Parkinson's disease and the initiation of the L-dopa treatment of this disorder. His chemical work in the freshly frozen autopsied human brain opened a new field of neuroscience research aimed directly at finding the neurotransmitter-related biochemical causes as well as rational treatments of neurological and psychiatric brain disorders.

Oleh Hornykiewicz

Some Thoughts on Memories

We all are slaves to our memories. Writing an autobiography has been rightly seen as a way of freeing oneself of the grip of the remembered past. In reality, committing memories, the good and the bad, to paper rarely achieves that goal. Too often is the written record a tangle of “fact and fiction.” True, many, perhaps all, events experienced in the past are deposited in our brain as accurate, lifelike pictures and episodes. However, only in some rare “moments of vision” are we able to draw on them: what we usually get when “calling to mind” the past are only various fragments of the real events. As a writer of your autobiography, you find yourself in the somewhat bizarre position of acting the part of interpreter of your own past. That is how our memories make the task of producing a useful, or meaningful (or true?), personal record so arduous a labor. We are indeed slaves to our memories. And yet, are not our memories said to be our second, possibly our only real, life?

Be that as it may, about six years ago, when Larry Squire—then as now Editor-in-Chief of the series *The History of Neuroscience in Autobiography*—asked me to contribute to Volume 2, I agreed, but, full of doubts, could not bring myself to write a single line. Asked a year or so ago to try my hand at it again, the sense of obligation, together with a touch of vanity, got the better of me, and here I find myself writing, foolishly, what I consider to be bits and pieces of my remembered past.

My Birthplace Sykhiv (Sichów)

All things considered, I have had a simple, uncomplicated life. Born on November 17, 1926, as the youngest of three boys into a fourth-generation family of Catholic priests (Eastern-[Byzantine] Rite Ukrainian Catholic; married priesthood), I spent my early childhood in a rural environment. Sichów, my birthplace (now Sykhiv), was a tiny community on the outskirts of Lwów (now Lviv), the capital of the then southeastern province of Poland, an area which until the end of World War I was a part of the Austrian Hapsburg Monarchy, known as eastern Galicia; in September 1939, Lwów became part of the Soviet Union and is now the westernmost provincial capital of the independent state of the Ukraine. In Sykhiv, my father served the

spiritual and sacramental needs of little more than a few dozen Ukrainian Catholic families; his main professional activities as youth educator were in Lviv, where he taught Catholic doctrine (including church history and philosophy) in high schools (gymnasias) and teachers' colleges. My mother, the descendant of an old and by then impoverished landed gentry, managed the (very modest) parochial economy and looked after the social and educational needs and well-being of the women folk and their young.

The picture of what for me represents my birthplace stands out clearly and distinctly in my mind—the parochial house, built by my father, where I was born; close by, surrounded by high fir trees, the little, nearly 300-year-old wooden church of The Holy Trinity, where I was baptized; the shady orchard with patches of pale-blue forget-me-nots in the tall, freely growing grass around the plum, pear, and apple trees; the large, sunny rose and flower garden behind the parish house, set up and lovingly cared for by my mother; and, separated from the fenced-in flower garden by a narrow dirt road, the small, but never still railroad station. All these were my early playgrounds, the world of my childhood.

Lviv (Lwów)

Moving to Lviv (in 1933 or 1934, at about the time of my reaching school age) was no shock to me. The bustling activity of the “big city” (about 200,000 inhabitants at that time) immediately captivated me, converting me forever into a confirmed city dweller. I liked school, and I was lucky to have had excellent teachers (in the Markian Shashkevych School). Many years later, when studying medicine in Vienna, I was once more to recognize how important good teachers were for one's (good) choices in life.

With warm feelings, I recall the long summer vacations, always spent in the country: the beauty of the mountains; the broad, inviting forms of the foothills; the wheat fields in the endless plains; the large, festive family gatherings; merriment with the innumerable cousins—I once counted more than 40, first degree, of them. Despite these holiday pleasures, I liked coming back to the busy city. Lwów of that time remains in my memory a cheerful place, full of joy of life and gaiety. The world as I saw it appeared to me a good place in which to be. Of course, I could not help noticing the homeless, the large number of street beggars, and the emaciated street acrobats, often using for their acrobatic stunts children my age and younger. Today, I would easily recognize behind all this the poverty, the misery and the despair. At that time, for me—the not-yet-teenager—all this was part of the world as it was, a world to be explored and looked at in wonder.

World War II, Part One (Lviv)

On September 1, 1939, the happy, carefree period of my childhood came abruptly to an end with the outbreak of the war, triggered by the German

attack on Poland. When after less than three weeks Poland surrendered to Germany, the non-aggression pact concluded a few weeks earlier (in August 1939) between Hitler and Stalin came into effect, and the Soviet army entered Lviv. Overnight, the gay, light-hearted city was transformed into a gloomy and desolate place: denunciations; arrests; dark rumors; a shortage of food; and endless political meetings (also for us school children), invariably ending with “spontaneous” messages of gratitude to Comrade Stalin. Quite desperate was the situation of the officers of the Polish army caught between two merciless enemies. I remember how one of them, our next-door neighbor (major of artillery), had been desperately beseeching my father—himself in a state of despair—to advise him what to do with himself and his family. Hardly 6 months later, more than 4000 Polish officers would be murdered at Katyn by Stalin’s secret police. Was our neighbour one of them? We never heard of him, of his wife, or their daughter (Halka; about my age) again.

My father immediately lost his job and faced the prospect of vanishing, like many members of the intelligentsia and the clergy, in Stalin’s dungeons or forced labor camps. We only were saved from that fate by my mother having Austrian ancestors. This entitled us to leave (hand luggage only!) the by now hermetically sealed off country, with Vienna as our final destination (where my father’s brother, our dearest uncle Myron, lived permanently).

Friends, home, hard-earned savings and possessions, and personal property and belongings, all that was left behind, never to be recovered. Not a bad lesson for a boy, just turned 13, about the vanity and futility of striving after security and material possessions.

World War II, Part Two (Vienna)

We arrived in Vienna, which (like the rest of Austria) was already part of Hitler’s Germany, in February 1940. Six months later, I started school again after overcoming the initial obstacle posed by my complete ignorance of the German language (which despite the Austrian ancestry raised doubt about my ethnic “suitability”) and my lung tuberculosis which I and my elder brother had contracted in one of the “resettlement camps” we had been staying at for months before we were allowed to go to Vienna. (As late as 1967, when I moved to Canada, I was required to go, for the first three years, to medical checkups [chest X-ray; sputum] at Toronto’s Gage [Environmental Health] Institute.)

After quickly getting a grasp of the German language, I plunged head over heels into the world of (printed) knowledge, literature, and poetry, now all wide open to me. But knowledge of German also acquainted me with Hitler’s political system and ideology; the hate propaganda against political, ethnic, and religious “enemies”; the absolute control of all media; no free speech; widespread fear of police informers and overzealous neighbors; and

again and again, people disappearing in the concentration camps. To me, now in my most susceptible and sensitive years, to watch the agony and despair of the Jewish population was deeply disturbing: to see their personal debasement, their defencelessness against being taken away, crammed in open trucks, to their final fate, the concentration camps. My father and my mother were appalled at what they saw and showed it to us, their children, unmistakably.

To my great relief, I found that school was mainly concerned with imparting knowledge rather than propagating Nazi ideology. In this, my school (the former "Sperlgasse"-Realgymnasium Wien II) may have been an exception. Before Hitler occupied Austria, the majority of pupils in this school had been Jewish (with Sigmund Freud, at one time, being one of them). By 1940, the Jewish pupils were gone, but their non-Jewish classmates and several moderate teachers had remained, and with them, the multi-ethnic spirit had also stayed. Apart from lessons on (ridiculously distorted) European history (hostile to Austria and the Hapsburgs), which could not be taken seriously, the most openly ideological subject taught was the new "race biology," presented to us with all the dangerous, because so scientific "genetic evidence" (and selected heritable diseases as examples); the implication of all this being that the "health and purity of the (Germanic) race" could be best preserved by eliminating all those carrying the "bad" and the "inferior" genes. When I see the present-day contagious enthusiasm for all research having to do with "the genes," and when I stop and think of the possibility of the "genetic mentality" coming, in whatever guise, to life again, I wonder and I worry.

As the eastern front began to crumble, huge crowds of refugees from the east poured into Vienna, adding to the many problems in the city. In 1943 and 1944, the bombing of Vienna began (Americans coming at daytime, British by night). This brought the until then distant war and the mountains of dead it had already cost right to my doorstep. Soon, our school was hit and we had to move to another school (which proved virulently Nazi), only to be bombed out of there again. Destruction and ruins were everywhere; I watched, stupefied, the Vienna State Opera House burn for two days and two nights. Much time was spent in (mostly inadequate) air-raid shelters which, when hit, turned into mass graves. In the end, death was everywhere, affecting practically every family, appearing more normal than staying alive. Paradoxically, it was the awareness of the "collective misery" that provided some alleviation of the personal grief—the only way one could keep functioning during that time. (To me, though, the loss of my elder brother three months after being sent, not yet 19 years old, to the eastern front has remained an open wound to this day.)

On April 5, 1945, the Soviet forces reached the outskirts of Vienna. The ensuing 9 days of fierce street fighting left nearly 40,000 dead soldiers (Soviet plus German) scattered in the streets and surrounds of the city. But then, the

nightmare of the Hitler regime was over, and we could breathe freely again and leave the darkness of the subterranean shelters; “it was from there that we emerged/to see—again—the stars” (Dante, 1980). During that period, on the eve of the final act, I concluded my high school education.

Horas Non Numero Nisi Serenas

My growing up in the shadow of World War II raises the question: What became of my youth, of what is said to be the “best years” of our life? Is it possible for me to recall anything of that time besides its horrors? Strange as it sounds, I find in my memory of that time many happy moments, which I do not think could be dismissed as a subconscious attempt at escaping from reality. I well remember the exhilaration of reading, in the original tongue, again and again the poetry of Schiller and Hölderlin and Goethe’s *Faust*, his *Wilhelm Meister*, and his *Wahlverwandtschaften*. To my mind come the evenings in the Vienna State Opera that step by step made me understand and love music—ever since my steady companion (along with poetry). I recall my fascination with Vienna’s historical past and the thrill of the first friendships. Also, there was the experience of nature, so plentiful around Vienna. With surprise I noticed how unmoved nature remained in the face of the war, continuing to give freely of her attractions. I can see with my mind’s eye in all intensity scenes such as lying on sunny summer days in the tall grass on the banks of the river Danube, daydreaming while watching the tug boats pass by, struggling up-river, smoothly gliding down or sitting on the slopes of the Wienerwald, so feminine in their soft contours, lost in thought, taking in the picture of the beautiful city below, resting there as in the hollow of one’s hand. What a wondrous thing our memory is! It registers, as Penfield (1975) tells us, every detail of our past experiences, yet when left to itself, it prefers—like the sundial—to count the sunny moments only.

Medical Studies

Initially, the political uncertainty at the end of the war, the desperate food situation (one of our best teachers, in German and Latin, starved during those months literally to death in his one-room flat near Vienna), and the continuous harassment by the Soviet authorities, so well described by Graham Green (1971) in his story *The Third Man*, produced a rather gloomy after-war atmosphere. But gradually, the positive influence of the newly gained freedom made itself felt and some aspects of normal life could be resumed.

It was in this atmosphere of the just beginning recovery from the total ruin and destruction that I enrolled, in October 1945, as a student of medicine at the University of Vienna. Before being admitted, however, we had to do something like two weeks of “rubble shovelling” (to help clean up

Vienna's ruins) and pass a medical checkup. When I stepped on the scales in the examining room, my weight was, to the doctor's alarm, not more than 48 kg (ca. 106 lb). Instantly, they gave me (for the whole term) a ticket for a free daily bowl of soup (provided for by the American Quakers).

My choice of "Medicine" was greatly influenced by my eldest brother who, seven years my senior, was already a medical doctor. Since I affectionately admired him, nothing appeared to me more desirable than being like him. Attending the lecture courses turned out to be no simple matter. Like the rest of Vienna, the medical buildings and lecture theatres were half in ruins, and the few intact ones were hopelessly overcrowded. There was a shortage of lab space and teaching staff. Everyone was trying to get his "Dr.med." (M.D.) as fast as possible, to be among the first to compete for the few paid internship positions in the city hospitals. The whole atmosphere—not necessarily conducive to good schooling—was that of a "struggle for the survival of the quickest."

Three Teachers

Three teachers in my medical years decisively influenced my research career. Friedrich Wessely, replacing the (for political reasons) dismissed professor of "Chemistry for Medical Students," was our teacher on that subject. A full-blooded, high-calibre organic chemist and Head of the University's Organic Chemistry laboratories, Wessely gained our affection by his uncompromising commitment to teaching. When at the end of the first winter term he noticed that we had understood next to nothing of his high-level chemistry, he gave us during the bitterly cold February 1946 term break an extra crash course, making us scribble on the blackboard all sorts of formulas, equations, and chemical reactions—with numb fingers, winter coats on, and all this for a full four weeks in the totally unheated lecture theatre.

Friedrich Ehmann was my teacher in neuroanatomy and brain development. Thin, kyphoscoliotic, short of breath, and cyanotic with heart disease, he was an example of competence, knowledge, and dedication. Exact and crystal clear, his lectures could have gone to print just as they were delivered. His standing phrase introducing important summary statements and conclusions, "la-dies-and-gentle-men-eve-ry-word-is-im-por-tant," became proverbial with us.

Finally, there was Franz von Brücke, our teacher in pharmacology and toxicology. Combining wide knowledge in both experimental medicine and biology with personal research experience and a special gift for speech, Brücke was able to communicate as no one else the excitement of pharmacological research and its relevance for the patient. With his classical education, ranging from ancient languages to literature to arts to philosophy, and his familiarity with the history of medicine, he succeeded in making us

realize how much medicine was part of the great human cultural endeavor, not just a scientific guest. Who could not be fascinated by his reading to us from Homer's *Odyssey* the lines pertaining to the use of opium ("one of the drugs given to the daughter of Zeus [Helen] by an Egyptian woman") for the purpose of alleviating mental suffering (Homer, 1991).

Vienna's Pharmacology, Part One

After obtaining my degree in medicine in July 1951, I immediately joined the Pharmacological Institute of the University of Vienna. It was for me an easy decision because the Head of that Institute was no other than Professor Franz von Brücke, my much admired teacher in pharmacology. For the first 10 months, though, I alternated between working from 3:00 PM to late at night in pharmacology as a "voluntary research assistant without salary" and serving from 7:00 AM to 2:00 PM as a "temporary intern" in the Rudolfs-Hospital. The clinical work earned me something like \$20 a month, which enabled me, at last, to go now and then to a café (coffee house) and twice a month on standing room or cheap seats to an opera or concert.

A Good Place to Visit

From Brücke's lectures, I already had an idea about the great tradition of the Institute, in its modern form established by Hans Horst Meyer, one of the internationally leading pharmacologists at the beginning of the last century. Thus, I was aware that Meyer's collaborators in this Institute included names to be found in every encyclopedia, such as George H. Whipple, Cornelius Heymans, Carl Cori, Otto Loewi, and Alfred Frölich. In the course of the 16 years I spent in that Institute, practically all prominent pharmacologists and physiologists of the time stopped in Vienna to visit our laboratories. I well remember Ernst Pick, Hans Heller, (Sir) Henry Dale, Carl Cori, Hans Molitor, Guiseppe Moruzzi, Otto Loewi, Wilhelm Feldberg, Cornelius Heymans, Stephen Kuffler, Hermann Blaschko, (Sir) John Gaddum, Harold Burn, Klaus Unna, Julius Axelrod, David Nachmansohn, and Henry Barcroft—the list could be continued *ad libitum*.

A regular visitor was Professor Ulf von Euler, the physiologist at Stockholm's Karolinska Institute, who had relatives in Vienna (of the same name). (I also remember the visit of his famous father, Hans von Euler-Chelpin, already in his 90s, and his wife, Baroness Ugges, Ulf's step-mother). On his visits, Ulf von Euler used to take friendly interest in my dopamine/Parkinson findings, ending the conversations—as many others in later years—with the remark: "Your discoveries should be recognized." I have always wondered what he meant by that.

A Good Place to Work

The great number of prominent visitors from around the world was not surprising considering the research that was being carried out in our laboratories. Practically all important branches of pharmacology were represented: heart and kidney; motor end plate, development of new muscle relaxants; hormone research; autonomic, especially catecholamine, and CNS pharmacology; drug metabolism and drug development (especially noteworthy were the studies on new broncholytics, using the guinea pig bronchospasm method, which became famous in connection with the discovery, made in our institute [Heribert Konzett, Richard Rössler], of the broncholytic activity of isoprenaline, furnishing the basis for Raymond Ahlquist's classification of adrenoceptors in alpha and beta type); EEG recordings and single cell recordings in the brain of awake rabbits; heart-lung preparations; and, last but not least, the application of the technique of sympathetic denervation of various organs and tissues. When, in 1961, Georg Hertting (from our Institute, later Head of Pharmacology at the Freiburg University, Germany) applied the latter method in Axelrod's lab in Bethesda, it provided the first and definitive proof of the presynaptic "re-uptake" of synaptically released noradrenaline (Hertting and Axelrod, 1961). This discovery fundamentally changed our concepts of synaptic neurotransmitter dynamics.

The Voice of a Dissenter

For young people like me, the prominent visitors, the high activity of the many research groups, and the atmosphere filled with ideas were greatly stimulating, giving rise to high motivation and enthusiasm for research. In the course of time, I found, however, one strong dissenter from my positive view of Vienna's pharmacology of the time. This was at a reception given by "Pergamon's" Captain Maxwell during the 1975 International Pharmacology Congress in Helsinki, at which also von Euler's pharmacological colleague at the Karolinska, known for his influence with the Nobel committee in physiology and medicine, was present. When I introduced myself to him, he greeted me with the words: "Vienna pharmacology?—a bad institution, no good research out of there." I thought this a somewhat subjective way of "evaluating" my former (or any other) institution, wondering about the reason behind the unusual choice of words for that wholesale stricture. But then, this episode allowed me to catch a (first) glimpse of the human factor even high-profile institutions and committees are burdened with.

My First Laboratory Work

I was introduced to experimental work by Adolf Lindner, Brücke's most senior assistant. Lindner was a friendly, fatherly person, good-humoured and open to relaxed conversations. He was a skillful experimentalist, and he

had a particularly inventive mind, holding many patents for novel therapeutic agents and procedures. Lindner's method of testing the aptitude of newcomers was to give them, without further help or comment, J.H. Burn's textbook (in English!) on *Biological Standardization* and let them chew on it (especially its statistics part). Many beginners would sooner than later quietly leave the lab, never to be seen again. It was on Lindner's advice that, years later, I applied for a British Council Scholarship that brought me to Oxford.

My first experimental work (together with the unforgettable Gustav Niebauer, later Head of Dermatology at Vienna's University) was on the enzymatic activity of human plasma, which we found to oxidize many polyphenols, including substances of physiological interest, such as dopa and the catecholamines formed from it. We termed this activity polyphenol oxidase and suggested that it contained copper as its prosthetic group. It soon turned out that our enzymatic activity was identical to the laccase activity of ceruloplasmin which Holmberg and Laurell had previously isolated from pig plasma. Important for my later work with the human brain and its diseases was a study I did together with the neurologists Heimo Gastagger and Helmut Tschabitscher on our copper-containing plasma enzyme in patients with Wilson's disease, a well-known disorder of copper metabolism with (hepato-lenticular) degeneration of the basal ganglia. In this disorder the polyphenol oxidase activity in the patients' plasma was low (like the levels of ceruloplasmin, as had earlier been shown by Scheinberg and Gitlin). Thus, it came about that, right in my first postdoctoral work, the influence of all three of my favorite teachers had made itself felt: Franz von Brücke (pharmacology, where I worked), Friedrich Wessely (my bent for chemical problems), and Friedrich Ehmann (my feeling at home in the human brain). Moreover, right in the beginning of my experimental research career, I came directly in touch with a biochemical problem in a basal ganglia disease. Was it only chance that, years later, this study proved a very useful introduction to my work on dopamine in Parkinson's disease brain?

The Oxford Interlude

Oxford Pharmacology

The 16 years of my stay in Vienna's Pharmacological Institute were interrupted by a stay, from September 1956 to February 1958, in the Pharmacological Department of Oxford University (with a British Council Scholarship), where I worked in Hermann (Hugh) Blaschko's laboratory. The department, under the direction of the very dynamic Professor Harold J. Burn, was at that time probably the most productive British pharmacological institution, humming with research activities and new ideas. Even before joining this Institute, I knew the names of its senior researchers: in

addition to Burn and Blaschko, Edith Bülbring (like Blaschko, an emigrée from Berlin), John Walker, Miles Vaughan Williams, and Raymond Ing (the chemist). The place was full of visiting scientists from all over the world. Since some of the senior members of Oxford's pharmacology were also members of well-known Oxford colleges, they often associated with distinguished scientists from abroad that were spending their sabbaticals in the respective colleges. I well remember the occasion when Professor Burn, a member of Balliol College, brought to lunch (regularly served in the department's library) a senior American visitor. Somehow, I found myself sitting next to him. Desperate to say something, I asked him what he was presently working on. Smiling, he replied that he was "trying to find out why the sky is blue." After that I kept my mouth shut, taking his answer as a rebuke for my silly question. Later, I learned that this was exactly what he was trying to figure out—his name was Harold Urey, the famous chemist from Chicago, the discoverer of deuterium.

*Meeting Fellow Scientists—and a Healthy Rule about
"Abstracts"*

Brücke, who obviously knew personally most of his British colleagues, gave me over a dozen letters of introduction; this enabled me to visit and meet personally senior researchers and heads of the main research laboratories in Great Britain. Other occasions to meet fellow scientists, both British and those from other countries working in British laboratories, were the famous meetings of the Physiological Society. I enjoyed the high level of the presentations and the lively discussions (with [Sir] Henry Dale and Edgar [Lord] Adrian still very much active). I also remember how impressed I was by the rule of the Society that gave its members the power to veto the publication of any of the "abstracts" (in the *Journal of Physiology*) of the papers just presented. I actually witnessed such a thing happen, when Sir Lindor Brown (physiologist, London) objected to an "abstract" on the grounds that it was "of no use." If the rule were made universal and applied today, I wonder what would happen to those fat volumes of "Abstracts" of the many oversized meetings, nowadays so popular.

Social Life

Of course, it would not have been the Oxford of the 1950s if, in addition to high academic activities, there would not have been an equally busy social life going on "day and night." There were countless receptions, dinners, and parties. The latter were civilized when given in respectable settings and, more often, less civilized (not to say, "wild") parties took place in the "digs" (private accommodations) of the younger (visiting) generation. I still have a vivid memory of the party at which one of our company made too

fast, “spirited” a start, and after about 90 min had to be “revived,” not too successfully, by being placed, as he was, in the bathtub filled with cold water.

Helping Blood Platelets to Take up Catecholamines

A few days after I arrived in Oxford (September 1956), Blaschko went on an extended lecture tour. During his absence, I kept myself busy by helping to measure adrenaline and noradrenaline uptake into isolated blood platelets in Gustav Born’s research lab (in the old Radcliff Observatory). Gustav was a combination of sharp scientific intellect, high musical talent (excellent flute player), and great sense of humor, soon becoming the world leader in blood platelet research. He was of great help to me in those first weeks of my stay in Oxford, introducing me to some of the peculiarities of that famous place.

Oxford, Continued: Dopamine Has Its Own Physiological Role in the Body

Blaschko’s Idea

When Blaschko returned from his lecture tour, he immediately started to draw my attention to dopamine, a substance so named just four years earlier by Sir Henry Dale, replacing the unwieldy 3,4-dihydroxyphenylethylamine or the misleading 3-hydroxytyramine. Until then, dopamine had been regarded as a mere metabolic intermediate in the synthesis of noradrenaline in the body. Blaschko, in contrast, conceived the idea that dopamine must have “some regulating functions of its own which are not yet known.” He expressed this idea in a lecture entitled “Metabolism and Storage of Bio-genic Amines,” which he had given in the fall of 1956 (on the occasion of Arthur Stoll’s, the famous Sandoz [Basel] chemist, 70th birthday) before the Swiss Society of Physiology, Biochemistry, and Pharmacology (Blaschko, 1957). Although Blaschko based his idea upon observations known to other prominent catecholamine researchers, such as Heinz Schümann and Ulf von Euler, none of them had come up with the right conclusion. This instance very aptly characterizes Blaschko: low key, kind, interested in people, and with an exquisite sense of humor. Blaschko had, in addition to a phenomenal memory, a very precise, penetrating mind, coming up with surprising solutions to seemingly insoluble problems.

Convinced of the correctness of his hypothesis, Blaschko asked me to test it experimentally. He referred me to experiments done 15 years earlier by Peter Holtz in Germany, the discoverer of dopa decarboxylase, who in 1942 had noticed that in the rabbit and the guinea pig, dopamine had an effect on the arterial blood pressure opposite to that of adrenaline: instead of raising the blood pressure, as adrenaline did, dopamine lowered it (Holtz

and Credner, 1942). Could this be due to dopamine having a physiological role different from that of adrenaline and noradrenaline?

My First Dopamine Study

Despite the Oxford busy social life, I found enough time to carry out Blaschko's idea. With my thorough training in Vienna's Pharmacological Institute, I found the experiments easy to do. When repeating the experiments of Holtz, I also used iproniazid, the first *in vivo* effective monoamine oxidase inhibitor. According to Holtz, inhibition of dopamine's metabolism by that enzyme should have abolished the, as he thought, "unspecific" vasodepressor effect of dopamine. However, I found that the opposite was true: iproniazid potentiated the fall in blood pressure produced by dopamine. I also tested L-dopa, the amino acid from which dopamine is formed in the body. L-dopa behaved exactly like dopamine. These results convinced both Blaschko and me that dopamine had its own physiological role in the body, different from that of the other two naturally occurring catecholamines, adrenaline and noradrenaline.

About six months later, my Oxford scholarship came to an end. Before leaving Oxford, in February 1958, to rejoin Vienna's Pharmacological Institute, Blaschko gave me the advice to continue working with dopamine, which he considered to have a "bright future." Blaschko's prediction was, once more, to come true, this time in my laboratory in Vienna.

Vienna's Pharmacology, Part Two: Mostly Dopamine and Mostly Parkinson's Disease

Focus on Brain Dopamine

Taking Blaschko's advice to heart, and having convinced myself of dopamine's own biological activity in the periphery, I thought it would be worth looking into dopamine's role in the brain. It so happened that my dopamine study in Oxford, which I had finished in early summer 1957, coincided in time with other dopamine studies that immediately focused the attention on the brain. In the August 3, 1957, issue of *Nature*, Kathleen Montagu from the Runwell laboratory in Wickford, near London, had reported, for the first time, on the occurrence of dopamine in the brain of various species, including humans. In the November 16, 1957, issue of *Nature*, Hans Weil-Malherbe, Head of the Runwell laboratory, followed up Montagu's paper by a study on the intracellular distribution of dopamine in the rabbit brain stem. At the same time, the antireserpine effect (in rabbits) of the dopamine and noradrenaline precursor L-dopa was for the first time described by Peter Holtz in Germany (in the September/October 1957 issue of *Naunyn-Schmiedebergs Archiv fuer Experimentelle Pathologic und*

Pharmakologic) and by Arvid Carlsson in Sweden (in the November 30, 1957, issue of *Nature*).

My decision to go into the brain was reinforced, practically immediately after my arrival in Vienna (February 1958), by reports published by both Carlsson in the February 28, 1958, issue of *Science* and Weil-Malherbe in the May 24, 1958, issue of *Nature* that confirmed once more the occurrence of dopamine in the animal brain and showed that reserpine removed the dopamine from the brain and that L-dopa restored its brain levels.

Starting with Brain Dopamine (in the Rat)

After my return from Oxford, I obtained my first fully salaried position in Vienna's Pharmacological Institute as a "Universitäts-Assistent," which entitled me to my own research group. However, for my first dopamine analyses, I lacked a sensitive detection apparatus, such as the just then developed Aminco-Bowman spectrofluorimeter. Therefore, I settled on the colorimetric adrenochrome reaction for catecholamines of von Euler and Hamberg, which I adapted for measurement of dopamine in brain extracts, combining it with the separation procedure for catecholamines developed in Carlsson's laboratory (Dowex columns).

The first study, which I did with my first postdoctoral collaborator Georg Holzer, dealt with the effect of monoamine oxidase inhibitors (iproniazid, harmine), as well as cataleptogenic agents (bulbocapnine, chlorpromazine), and cocaine on dopamine levels in the whole rat brain. We found that only monoamine oxidase inhibitors changed (increased) brain dopamine; the time course of the effect suggested a rather high turnover rate of the dopamine in the rat brain. This we interpreted as favoring a physiological role of the amine in brain function.

The Emergence of the Dopamine/Parkinson's Disease Idea

What could be the role of dopamine in brain function? In the January 15, 1959, issue of *Experientia*, Bertler and Rosengren (from Carlsson's laboratory in Lund) published an exciting observation. Patterning themselves on Marthe Vogt's exemplary study on the regional distribution of noradrenaline in the dog brain, Bertler and Rosengren found, also in the dog, that dopamine, in contrast to noradrenaline, was highly concentrated in the corpus striatum (Bertler and Rosengren, 1959a). This observation immediately gave brain dopamine a functional significance. Connecting the striatal localization of dopamine with the brain dopamine-depleting and parkinsonism-inducing effects of reserpine, it now was possible to say, as Bertler and Rosengren did, that the "results favour[ed] the assumption that dopamine is connected with the function of the striatum and thus with the control of movement."

For me, the direction of my own research was now very clear. With all the evidence available from animal experiments, the one thing that needed to be done was to leave the animal brain and the reserpine model and go directly to the human brain. As it soon turned out, this was the decisive step. I was already familiar with basal ganglia, i.e., Wilson's disease from my first postdoctoral work in the early 1950s; and my very recent dopamine/L-dopa studies in Oxford and now in Vienna was just the right introduction to this as yet uncharted field of research. Thus, the idea of connecting the observations from laboratory animals with human basal ganglia diseases, especially Parkinson's disease, came—after reading the Bertler and Rosengren 1959 *Experientia* report—very naturally to me. In the same year, Carlsson's report on the Bertler and Rosengren data appeared in the *Pharmacological Reviews* (vol. 11, part II). However, much to my regret, I could not benefit from any of Carlsson's ideas; by the time his article came out in print (end of June 1959), we in Vienna were already well into our Parkinson/dopamine work, with results in the first two patients (low striatal dopamine) already in our hands.

Fresh Postmortem Brain Material: Its Rise from the Scorned to the Most Treasured

At the time when I started working with fresh autopsied human brain, studies in such material of chemically unstable neurotransmitter substances, including catecholamines and their related enzymes, had been rare. They had been traditionally viewed with great suspicion as to their usefulness and scientific significance. Many senior colleagues, including knowledgeable biochemists, tried to dissuade me from “wasting my time on such half-decomposed, dirty material.” However, this was the only material that could possibly be used for the study I had in mind. Today, fresh human brain material is highly valued as a source of information on human brain diseases that cannot be obtained from animal models. Several human brain tissue banks in many countries now exist, supplying research labs with sometimes very rare and precious material. This radical reversal of opinion has been primarily the result of the unexpected success of our dopamine studies in the Parkinson brain and the subsequent introduction of dopamine replacement with L-dopa.

The Dopamine/Parkinson's Disease Work Begins

The Source (of the Material)

In order to carry out my project, a suitable source of fresh autopsied human brains had to be found. It was not difficult to obtain autopsied non-neurological control brains from the University's Pathological Institute.

The best source for Parkinson material was the pathology unit of Vienna's largest City Hospital "Wien-Lainz" with its attached large Home for the Aged, where many Parkinson patients were chronically housed. However, the clinician in charge of the neurology unit of that nursing facility, Walther Birkmayer, was not on the best of terms with me at that time. Fortunately, my next postdoctoral collaborator in training, replacing Georg Holzer, was Herbert Ehringer, a very capable, hardworking, and ambitious young man. What made Ehringer so essential was that he had, from his student days, a good relationship with the chief prosector of the "Lainz" pathology, Stephan Wuketich, who readily agreed to supply us with the necessary brain material.

The Discovery

In April 1959, about eight weeks after reading the Bertler and Rosengren report in *Experientia*, we received the first brain of a patient who had died with Parkinson's disease. After carrying the samples of the caudate nucleus and putamen of this patient, together with control samples, through the extraction procedure, the thrilling moment of performing the von Euler and Hamberg color (iodine) reaction arrived. Instead of the pink color in the control samples, indicating presence of dopamine, the reaction vials containing the Parkinson material showed hardly a tinge of pink discoloration. For the first time ever, and before even placing the reaction vials into the colorimeter, I could see the brain dopamine deficiency in Parkinson's disease literally with my own naked eye!

The Study

By late spring of 1960, within little more than 12 months, we had collected and analyzed the brains of 17 non-neurological controls; 2 patients with Huntington's disease; 6 patients with extrapyramidal disorders of unknown etiology; and 6 Parkinson brains (4 postencephalitic, and 2 idiopathic disease). Two neonate brains and one infant brain were also examined. Of all the 14 cases with extrapyramidal disease, only the 6 Parkinson's disease cases had a severe loss of dopamine in the caudate nucleus and putamen. The results of this study were published in the December 15, 1960, issue of the *Klinische Wochenschrift*. Ever since that time, this discovery has provided a rational basis, and a point of departure, for all the following modern research into mechanisms, causes, and treatment of Parkinson's disease.

It is worth noting that our observations were made by means of a simple, only moderately sensitive, colorimetric method; they did not require any complicated, ultra-modern machinery or out-of-the-way chemistry. This shows that sophisticated methodology, although sometimes of great help, is not an essential component of discovery. The simple method we had used matched perfectly the clear idea on which the study was based, resulting in that irreducible simplicity that is an unfailing mark of the true and durable.

On Conceiving an Idea: The Beginnings of the L-Dopa Era

The discovery of the dopamine deficiency in the Parkinson brain was, quite logically, the basis for the next stage of what came to be known as “the dopamine miracle,” that is, the step from the human brain homogenate to the patient. This step marked the beginnings of the dopamine replacement era of Parkinson’s disease treatment with L-dopa.

It has often been noted that even what later appears as an obvious idea requires the right moment to be conceived. In mid-October 1960, two months before our report on the dopamine discovery came out in print, the idea struck me that it should be possible to improve the motor deficits of Parkinson’s disease by replacing the missing brain dopamine. At that time, I was revisiting Blaschko’s laboratory in Oxford, among other things correcting the proofs of our dopamine paper, which had been forwarded to me from Vienna. Was it the influence of the ideas—still lingering in the lab’s atmosphere?—of my previous dopamine/L-dopa work done there that put the instant thought into my mind of using L-dopa as the dopamine-replacing drug of choice in the patients? What a splendid neurophilosophical topic would the true life of ideas, and the world they inhabit, make!

Looking for a Neurologist: On the Usefulness of Vienna’s Cafés

In order to carry out my idea, I needed the help of a neurologist. My immediate choice fell on Walther Birkmayer. Birkmayer was a clinical neurologist with a sharp diagnostic eye and considerable drug-testing experience, especially with anticholinergics in Parkinson patients. Since he was in charge of the neurological ward of Vienna’s largest Home for the Aged Wien-Lainz, he had access to many chronically housed patients with parkinsonism. Birkmayer had an engaging personality and was easy to motivate, and, in addition, he was very eager to find a way into research. These qualities suggested him to me as an ideal partner for carrying out my L-dopa idea. On the other hand, Birkmayer had many enemies in Vienna’s medical faculty (especially because of his political past); therefore, it required an act of balance to work with him and yet remain on good terms with the others.

Following the first successful L-dopa trials, Birkmayer and I had five years (1961–1966) of a productive and amicable working relationship. We regularly met, sometimes twice weekly, in order to plan the next set of the rapidly progressing clinical trials. I taught Birkmayer monoamine biochemistry, myself turning into something like a clinical pharmacologist. Initially, we met in my office in the Pharmacological Institute, but after a while Brücke disliked Birkmayer’s presence in “his” Institute. We then moved our sessions to the “Café Schwarzspanier,” not an uncommon Viennese answer to

all kinds of space problems. In the past, several Viennese artists/bohemians had been known to have actually lived in cafés; one of them, a noted writer, even ended his life in his café. The Café Schwarzschaner was a very convenient meeting place for me, as it was located in a housing complex just around the corner from the Pharmacological Institute. On the site of the housing complex stood, until 1903, the house in which Beethoven had spent the last 18 months of his life and in which he died in 1827. The Café Schwarzschaner also is no more; it closed its doors sometime in the 1970s.

It Is Impossible to Suppress an Idea

Tyrants, dictators, and oppressive regimes are all well aware of, and bemoan, the fact that ideas, once brought into the world, cannot be indefinitely suppressed, let alone killed. This is also attested, on an infinitely smaller scale, by the initial fate of my L-dopa idea.

At the beginning of November 1960, immediately after returning from my visit with Blaschko, I contacted Birkmayer about the possibility of an L-dopa trial on his ward. Despite the clear rationale for my proposal, Birkmayer would not listen to me. There were two reasons for that. First, at that early time, dopamine as a chemical compound of physiological interest, as well as its possible involvement in basal ganglia function, was quite alien to Birkmayer's thinking. Second, his unwillingness to collaborate with me went back to a grudge he bore me when in the spring of 1958 I rejected, with a flimsy excuse, his suggestion to analyze the brains of patients with Parkinson's disease, coming to autopsy from his ward, for changes in hypothalamic serotonin, an idea that to me lacked scientific stringency.

After several reminders and pressure "from above," especially from Brücke, in July 1961, nearly nine months later, Birkmayer finally gave L-dopa intravenously to his first few patients. The intravenous (iv) route suggested itself for two reasons. First, it was the most economical route, considering the small amounts (about 2 g) of L-dopa with which I was able to supply Birkmayer. Second, iv L-dopa had been tried in humans as early as the 1940s and found basically safe. In the immediate past, Degkwitz, a neuropsychiatrist at the University of Frankfurt in Germany, had used iv L-dopa in an attempt to counteract, *inter alia*, the reserpine "sedation" in psychiatric patients.

The Dopamine/L-Dopa Miracle

The effect of iv L-dopa in our first patients was spectacular. Akinesia, the most disabling of the motor deficits, responded most dramatically. Birkmayer instantly forgot his grudge against me and became a zealous convert. We started our first L-dopa trials in July 1961. In August, we made

a documentary film with five patients. Eight weeks later we sent in our first report entitled "The L-Dopa Effect on Akinesia in Parkinsonism" to the *Wiener Klinische Wochenschrift* for publication. This report appeared in print in the November 10, 1961, issue of the journal. In the evening of the same day, I presented in the scientific session of the "Gesellschaft der Ärzte in Wien" for the first time my dopamine/Parkinsonism brain study in a lecture with the title "Biochemical-Pharmacological Foundations of the Clinical use of L-Dihydroxyphenylalanine in Parkinsonism." My lecture was followed by Birkmayer showing the film and commenting on the clinical observations.

Today, it is generally agreed that the initiation of the treatment of Parkinson's disease with L-dopa represented one of the triumphs of pharmacology of our time. L-dopa's unprecedented success proved, for the first time, that therapeutic neurotransmitter replacement in a chronic, progressive, degenerative brain disease (until then regarded as basically untreatable) was indeed possible. This provided, apart from the benefit to the patients, a stimulus for analogous studies of many other brain disorders, both neurological and psychiatric. As John Hardy (National Institutes of Health, Bethesda) put it in a recent letter to me, "L-dopa's discovery was the defining finding for transmitter-based therapeutics."

The Simple and Logical Is Not Always the Most Obvious

I have stressed the logical, rational nature of the steps leading to the discoveries about dopamine and L-dopa in Parkinson's disease. Easy as they were to take and carry out, at that time, these steps were not as obvious to everyone as they appear today. Two of the most striking examples may serve to illustrate this point. First, in Carlsson's laboratory in Lund, Bertler and Rosengren followed up their crucial January 1959 study in the dog by measuring, without delay, dopamine in the normal human postmortem brain (Bertler and Rosengren, 1959b). However, they apparently did not attempt to obtain and analyze Parkinson brains, despite the fact that pathological material is easier to obtain than brain material from control cases. Second, in 1960, Degkwitz, as mentioned, had used iv L-dopa in psychiatric patients (Degkwitz et al., 1961). He was the first to show that L-dopa abolished the reserpine "sedation" in humans—a state that must have included the well-known reserpine akinesia. Stangely enough, the idea of trying to counteract the Parkinson akinesia with L-dopa had not occurred to him. Both these examples clearly illustrate how restricted, one-way thinking can influence the direction of one's work. At that time, not only leading dopamine laboratories, but also knowledgeable clinical experimenters were so deeply preoccupied with reserpine and its central actions, be it in animals or in patients, that all of them overlooked and missed the most obvious.

All Too Human?

The amicable and highly successful working relationship between Birkmayer and me, which could have turned into something like friendship, did not last. In the course of time, Birkmayer, who could have rested on his own major clinical achievements, developed his own version—contrary to historical fact—of the events leading to the use of L-dopa. Taught as I had been to respect the academic code and to acknowledge other people's work and ideas, I found Birkmayer's behavior discouraging, and I put our relationship on ice. It is amazing to see how often this disregard of intellectual property repeats itself, right to this day, in academic circles. To see this happen has always been deeply saddening to me. Is it the lack of proper judgement or an unhealthy ambition that drives people to such behavior? Or is this due to a slow subconscious process of reinterpretation of reality in one's own favor, to the point of the individuals, in fact, believing in what they are saying? How difficult is it to read and understand the hidden thoughts and motives of others—and how much could be said about it!

Dark Days and Years for Dopamine

The quick success of the steps "from brain homogenate to treatment" would have been expected to immediately establish brain dopamine's role in brain function, particularly in Parkinson's disease. This, however, was not the case. Despite all the evidence from animal experiments, especially those with reserpine, and the human brain, especially Parkinson's disease—both of which I found to be compelling—it took many years before dopamine was recognized as a brain neurotransmitter in its own right and its role in Parkinson's disease was accepted. Why was this so?

The main reason for the neglect of brain dopamine in the first half of the 1960s was the controversy, starting around 1956, between Bernard Brodie (NIH, Bethesda) and Arvid Carlsson (Lund/Göteborg) about how to explain reserpine's central "sedative" or "tranquilizing" effects. Brodie had advanced the brain serotonin hypothesis, whereas Carlsson saw more reason for the role of brain "catecholamines." Today, it is difficult to understand why the discoveries about brain dopamine, made between 1957 and 1960, had not immediately put an end to the debate, or at least changed it into a "serotonin-dopamine" dispute. Quite to the contrary, the debate continued well into the mid-1960s, with dopamine, if not completely ignored, being lumped together with noradrenaline as "the catecholamine(s)." Also, the existence of dopamine receptors in the brain, distinct from noradrenaline receptors, was sometimes forgotten. Also, dopamine's crucial and so plainly evident role in reserpine parkinsonism and Parkinson's disease was for several years discredited by the claim that the direct (synthetic) noradrenaline precursor 3,4-dihydroxyphenylserine (dops) actually had central actions

similar to those of L-dopa. Curiously, it was Marthe Vogt, probably the astutest brain researcher of the time, but not particularly a friend of dopamine, who in 1960, during one of the fiercest battles, had the insight to remind the combatants that one "could explain the effect of dopamine on an entirely different basis from the effects of the other catecholamines. . ." and therefore she was "not quite certain that we are right in lumping together experiments in which the [brain] dopamine level is up and others in which the noradrenaline level is up" (Vogt, 1960).

Coming to the Rescue of Brain Dopamine

I felt very unhappy about so many influential people being so deeply pre-occupied with this debate. My attitude was that of a "dopamine purist." I did not see any need for any other monoamine, be it serotonin or noradrenaline, in order to explain Parkinson's disease and reserpine parkinsonism (in the debate usually misnamed "reserpine sedation" or "tranquilization"). I felt that any "admixure" was detrimental to the significance and uniqueness of all the dopamine/L-dopa observations. However, my opinion was not sufficient to change the minds of the "dogmatists." Fortunately, I found two strong allies: Theodore (Ted) Sourkes and Guy Everett.

Ted Sourkes, at McGill's Allan Memorial Institute of Psychiatry in Montreal, was a seasoned catecholamine researcher with a long, distinguished record. He came early to the brain dopamine field when, in 1961, he found, together with the clinical neurologist André Barbeau (of the Université de Montreal), low urinary excretion of dopamine in patients with Parkinson's disease and, as a consequence of that, suggested to Barbeau (independently from us in Vienna) the oral use of L-dopa. After that, Sourkes and the neurophysiologist Louis Poirier (of Laval University in Quebec City) were the first to reproduce, in the primate, the main symptoms of parkinsonism by lesioning the substantia nigra, correlating them with the dopamine loss in the striatum, and thus producing evidence for a nigrostriatal dopamine pathway in the primate.

The other strong dopamine advocate, Guy Everett, was the neuropharmacologist at the Abbot Laboratories in Chicago. In a series of pharmacological experiments (in rodents), Everett demonstrated that locomotor behavior was under the control of brain dopamine, with no involvement of noradrenaline. By this, he also disproved the notion that dops, i.e., the noradrenaline formed from it, had L-dopa-like central effects. He also coined for the mistreated dopamine the term "the Cinderella of the biogenic amines" (Everett, 1970). Since both Sourkes and Everett were competent and highly respected researchers, their observations could not be lightly dismissed. But in the end, the fruitless "serotonin-catecholamine" debate was terminated and decided in favor of brain dopamine by the unprecedented success of the L-dopa therapy.

“You Have Got the Necessary Brains”: Human Brain Studies, Continued

When, in the summer of 1961 Ted Sourkes visited me in Vienna, we also discussed the difficult dopamine situation. In the course of the discussion, I asked Ted, in passing, whether he thought it worthwhile for me to continue with the human brain studies. “Yes, carry on with this work,” he said, humorously adding, “you have got the necessary brains for it.” Thus encouraged, we continued this line of research and found the results quite rewarding.

At the end of 1960, Ehringer moved to the University of Innsbruck and was replaced by Hanno (Hans) Bernheimer, who was very good with chemical methodology and a skillful brain dissectionist. With his help, I concentrated on what I thought was important. I provided evidence for the existence of a nigrostriatal dopamine pathway in the human brain, at that time shown only in animal brain. We showed, by measuring dopamine’s metabolite homovanillic acid, that in Parkinson’s disease the remaining dopamine neurones in the striatum were highly overactive; this observation gave rise to the very familiar concept today of the compensatory (adaptive) capacity of the remaining neurones, so as to maintain striatal function despite major neuronal losses. We compared, in a large collaborative study, the degree of substantia nigra cell loss with the loss of striatal dopamine and established a cause-effect relationship between the severity of Parkinson symptoms and the degree of striatal dopamine loss; we also demonstrated this by studying the dopamine levels separately in the right and the left striatum in a case with unilateral parkinsonism. With Hans-Jörg Lisch (who replaced Bernheimer in 1966), I traced the course of the nigrostriatal dopamine neurons in the human brain by studying the distribution of homovanillic acid within the internal capsule. Last, but not least, we showed, together with Walther Birkmayer, that the L-dopa effect in the Parkinson patient was specific and not mimicked by any of the other catecholamine- or L-dopa-like substances, including the ill-famed dops.

No Language Barrier for Brain Dopamine

Scientific work published in the Western World in languages other than English is said to be at risk of being totally ignored. This cannot be said of our observations published in German; they immediately attracted the attention of many English-speaking colleagues. In February 1961, only eight weeks after our brain dopamine/Parkinson paper came out in print, Ted Sourkes contacted me by letter, and a couple of weeks later, so did André Barbeau. Many others wrote to me asking for information; among them were Bill (W.G.) Clark, Charles Markham, David Marsden (at that time still a medical student), Pat McGeer, Isamu Sano, Erminio Costa, Michael Pare,

Everardus Ariens, Morris Aprison, Guy Everett, Mel Yahr, Wilhelm Raab, Harold Himwich, Donald Calne, George Selby, Sidney Udenfriend, and Melvin vanWoert. The first visitor was Ted Sourkes, who in August 1961 already came to Vienna to see me in my laboratory. In September 1965, I had a visit from Melvin Yahr and Roger Duvoisin (from Columbia University's neurology department). Other visitors, as far as I remember, included André Barbeau, Merton Sandler, Leo Hollister, and Melvin vanWoert.

Bill Clark, the biochemist turned (psycho)pharmacologist in Los Angeles, proved himself a diligent reader of (German) footnotes. In his letter of January 28, 1964, he asked me for the L-dopa film, which we had offered on a loan basis to interested people in a footnote in our 1962 paper written in German. He showed the film to his neurological friend Charles Markham, who, in April 1964, wrote to me, saying that "there is no question that the second and third patient showed greater mobility after L-dopa." Markham, a highly successful and very circumspect L-dopa expert, was among the first in the United States to use oral L-dopa.

In 1966, Donald Calne became seriously interested in repeating our iv L-dopa trials in London. He wrote and asked me about the best source of L-dopa for iv use. A little later, Calne was the first in Great Britain to publish on the therapeutic efficacy of oral L-dopa and the first to demonstrate, in 1973, the anti-Parkinson action of bromocriptine, the first clinically useful dopamine agonist. Donald and I became close friends in the course of our wanderings that brought us both to Canada: Donald to Vancouver and me to Toronto.

When vanWoert came to see me in October 1966, he gave me a copy of an as yet unpublished manuscript, written together with George Cotzias and L.M. Schiffer, reporting their spectacular results with high oral doses of D,L-dopa given to Parkinson patients in daily increasing amounts. Reading this report, which subsequently came out in the February 16, 1967, issue of *New England Journal of Medicine*, I realized that at last L-dopa had reached the New World.

First Contacts With the New World

The New World opened its doors to me for the first time in November 1965. Sidney Udenfriend (NIH, Bethesda) had sent me an invitation on behalf of Melvin Yahr and Erminio Costa, who were organizing a symposium on the "Biochemistry and Pharmacology of the Basal Ganglia." This was on the occasion of the opening of the William Black Lecture Hall at Columbia University's Parkinson's Disease Information and Research Center in New York City. It was at that symposium that I gave my first formal North American lecture (followed by an interview with the press, together with Arvid Carlsson) on my work on dopamine, L-dopa, and Parkinson's disease. However, already two weeks earlier I had spoken about our results in a

seminar in Canada, little knowing that soon this country would become my second (or third?) home; this was upon Ted Sourkes' invitation, who had asked me to speak in his lab at Montreal's Allan Memorial Institute of Psychiatry at McGill.

At the Columbia symposium in New York I was greatly impressed with meeting so many prominent North American scientists. "A sky full of stars." There were such senior people as Herbert Jasper of the McGill Neurological Institute, Columbia's Houston Merritt and David Nachmansohn, Wally Nauta (from MIT, Boston), Seymour Kety (from NIH, Bethesda), George Koelle (University of Philadelphia), and George Palade (Rockefeller University, New York), among others. Brodie, Udenfriend, Costa, and Carlsson were already known to me from the serotonin-catecholamine debates. I knew Sourkes and Yahr from their visits to my Vienna laboratory. I met Everett there for the first time. Mel Yahr, the main organizer of the symposium, was the first neurologist worldwide to test (in 1968/1969) the anti-Parkinson efficacy of L-dopa in a double-blind study. He became the leading neurologist, and the driving force, of clinical Parkinson's disease research, first at Columbia and then at New York's Mount Sinai School of Medicine. Mel and I developed a close, friendly relationship over the many years of our continuous contacts and exchange of ideas.

Trying to Put Dopamine on the Agenda of "Big Labs": Support from an Unexpected Direction

The Columbia meeting was also the starting point for a collaboration between Sidney Udenfriend at Bethesda and me in Vienna. At that time, Udenfriend was studying and characterizing, for the first time, the enzyme tyrosine hydroxylase. He agreed to measure this rate-limiting enzyme in our human normal and Parkinson brains. For several months I was supplying him with postmortem brain material. However, there were, at that time, too many technical problems with measuring the enzyme in human postmortem material which could not be solved on such an across-the-Atlantic basis. However, we continued our friendly relationship and years later shared, to our pleasant surprise, the Research Award of the City of Hope National Medical Center, Duarte (Los Angeles), where Eugene Roberts, of GABA fame, was Head of Neurosciences, and the wonderful Rachmiel Levine was Research Director.

Another important collaboration I had started in the mid-1960s was that with Rolf Hassler, the eminent Parkinson researcher and director of the Max-Planck Institute for Brain Research in Frankfurt, Germany. Hassler kept supplying me with brain samples taken from cats in which he had made various midbrain, including substantia nigra, lesions. However, when, in 1965, I voiced the view that there existed, in humans, a nigrostriatal dopamine pathway, Hassler terminated all contacts with me: he was strictly

opposed to the idea of such a fiber connection. Years later we established tacitly a truce, but to my regret never regained our former easy relationship. What a pity to lose over such matters a potential friend!

While my attempts to put dopamine and Parkinson's disease on the agenda of internationally highly respected laboratories had, at most, doubtful results, the cause of brain dopamine received support from an unexpected direction. In July 1964, George H. Acheson (University of Cincinnati, OH), the Editorial Chairman of the renowned *Pharmacological Reviews*, asked me to write an article on "the interesting aspects of dopamine in the brain." He stressed that the article should point to the future rather than review the past. My essay, which I boldly entitled "Dopamine (3-Hydroxytyramine) and Brain Function," appeared in June 1966. It was indeed written for the future, putting brain dopamine definitively on the map of brain research at a time when the word "neuroscience" was not yet what it is today. I consider this article as the successful conclusion of my "human brain dopamine era" in Vienna's Pharmacological Institute. To this day I admire Acheson's foresight in requesting such a review in the "darkest days" of dopamine. It shows how a good editor can decisively help in advancing the progress of research and influence its direction.

Enough Time for Some "Real" Pharmacology

During all those dopamine/parkinsonism years, there was enough time to do some "real" pharmacology. Together with Ehringer and Klaus Lechner, we studied the effect of neuroleptics on the catecholamine and serotonin metabolism in the rat brain. With Alfred Springer and A. Aigner, I examined the effect of inhibition of dopamine- β -hydroxylase on the locomotor effects of L-dopa. Adrenergic tolerance was investigated with Hubert Obenaus (who later became Head of Toxicology at Vienna's Sandoz Research Institute—and godfather of one of my children). And with Walter Kobinger (Later Director of Pharmacology at the Ernst Boehringer Research Institut in Vienna), we studied the role of medullary cholinergic mechanisms in the regulation of the carotid sinus reflex and blood pressure. We developed an intricate method for injection of drugs into the internal carotid artery in the rat (later used in the Netherlands by my Vienna collaborator Pieter van Zwieten). Ever since, Walter and I have continued and deepened our close and friendly relationship.

My 10 Years in Toronto (1967–1977)

In the fall of 1967, I received an offer from the University of Toronto. Although at that time Brücke was in reasonably good health and about 10 years from retirement, people in the Institute were already getting into the starting holes for the race for his position. It was as if they had sensed that

Brücke's post would soon be vacant. (Brücke died, unexpectedly, two-and-a-half years later, in the spring of 1970.) The relaxed atmosphere in the Institute, so typical and enjoyable until then, changed. Since I have never been good at races for positions, I welcomed the opportunity to move to Toronto to become, to my own surprise, a (neuro)psychopharmacologist.

The way I came to psychopharmacology was very simple. In September 1966, Toronto's pharmacologist Werner Kalow had heard me speak on my dopamine/parkinsonism work at the Biberach (Germany) laboratories of Boehringer Ingelheim (where, for a year or two, he, Kalow, was Director of Medical Research). He contacted Harvey Stancer, the biochemical psychiatrist at the just then opened Clarke Institute of Psychiatry at the University of Toronto. Soon afterward, I was offered the position of Head of the Clarke's (as yet completely empty) Psychopharmacology Division. I accepted, and thus, thanks to dopamine, I could rightly call myself, for at least 10 years, something like a psychopharmacologist. (Here I may add that I was not completely unprepared for that position. A few years earlier, I had written, together with Brücke, a book on the *Pharmacology of Psychotherapeutic Drugs*, published in 1966 in German and in 1969 in English.)

I moved to the North American continent at the best possible time. In February 1967, George Cotzias published his landmark report on the strong, sustained anti-Parkinson effect of high oral doses of D,L-dopa (Cotzias, van Woert, and Schiffer, 1967). This produced quite a stir in the North American neurological research community. Thus, when 10 months later, in October 1967, I made a fresh start in Toronto, the atmosphere was just right for my interest in dopamine and Parkinson's disease.

New World, New Colleagues

Settling down in Toronto was made easy for me by the very helpful attitude of the colleagues at the Clarke Institute (with the always available Harvey Stancer next door in the neurochemistry section), as well as in the departments of pharmacology and neurology. I was soon appointed full professor with tenure in pharmacology and later in psychiatry. I immediately liked the atmosphere in the Clarke Institute and its just then appointed new Director Robin Hunter (also Head of the Department of Psychiatry), whose honest and straightforward character suited me. Werner Kalow, now the newly appointed Head of the Pharmacology Department and pioneer of the new research field of "pharmacogenetics," greatly contributed to my own and my family's feeling of being at home in Toronto; for newcomers like us, his advice and help with the smaller and bigger problems were invaluable. I liked and respected Clifford (Rick) Richardson, Head of the University's Neurology Department. He was a real gentleman, kind, modest, and self-disciplined, and his name was already known to me from the "Steele-Richardson-Olszewski Syndrome" (progressive supranuclear palsy). With the active help

of the people in Toronto, as well as throughout the United States and Canada (e.g., Ted Sourkes in Montreal), I soon found my way around North America. I liked and admired the enthusiasm and the open-mindedness of my fellow scientists and their readiness to recognize and acknowledge other people's achievements. I could not have wished for better colleagues.

More New Colleagues

I was surprised at how quickly my presence in Toronto was detected. Soon, I had to satisfy innumerable requests for invited lectures and research seminars, organizing committee meetings, congresses, and symposia all over the North American continent; sitting on grant committees, going on site visits, and evaluating grant applications for the MRC (Canada) and the NIH; and more than half a dozen memberships of medical advisory boards of various foundations. In the latter capacity, I was able to meet with practically everyone prominent in neuroscience in North America. There was Milton Wexler's "Hereditary Disease (H.D.) Foundation" in Los Angeles; Sam Belzberg's "Dystonia Research Foundation" (with John Menkes [Los Angeles] as Research Director); the "Committee to Combat Huntington's Disease" in New York with Marjorie Guthrie, the admirable and lovable wife of Woody Guthrie; and several Parkinson's Disease Foundations, both in Canada and in the United States. In addition, there were the lay patient societies and organizations. To all this should be added the visitors that came to see me at the Clarke Institute to discuss questions of mutual interest. I remember the day when Hirotaro Narabayashi, the renowned neurologist (from Tokyo), came to see me (when visiting his neurosurgical colleague, the admirable Ron Tasker, at the Toronto General Hospital). Narabayashi's visit was the beginning of our very close relationship that lasted until his death in 2001. Seymour Kety, one of the great "fathers of neuroscience," I had met already at Mel Yahr's symposium in 1965. Subsequently, I came to admire Kety's clear and unerring judgement, his wide horizon, and his ability to see things in a larger context. His "knowledge of things" and awareness of its philosophical underpinnings made many of our conversations a special pleasure and gain for me.

Research at the Clarke Institute's Division of Psychopharmacology

It was easy for me to do research at the Clarke Institute. I found that the colleagues in the other research sections, most of them psychiatrists, were very pleasant people with whom I soon developed friendly relationships and from whom I learned a great deal about that dimension of the human brain that we could not claim to see or measure (yet) in our test tubes.

The Right Drug for the Wrong Reason?

I soon resumed my dopamine/Parkinson research work. This became, in my view, a necessity when I noticed that seasoned brain researchers, who had spent all their lives tackling frustratingly difficult problems, found the whole brain dopamine/Parkinson business irritatingly simple and the dopamine-substitution explanation for L-dopa's "miraculous" effect outright unbelievable. Catchy, but distinctly jaundiced phrases were coined by distinguished brain scientists, such as that L-dopa was "the right therapy for the wrong reason" (Ward, 1970; Jasper, 1970). Doubts about L-dopa as a physiological replacement of dopamine were expressed by stating that "since L-dopa floods the brain with dopamine, to relate its [antiparkinson] effects to the natural function of dopamine neurons may be quite erroneous" (Vogt, 1973). Failure of some investigators to detect in the human brain significant activity of dopa decarboxylase, the enzyme responsible for dopamine formation, appeared to justify the skepticism. Challenged by these doubts, the first problem I attacked was the presence of dopa decarboxylase in the human brain. With my extremely motivated and able Ph.D. student, Kenneth G. Lloyd, who came to me from Ted Sourkes' laboratory, we demonstrated that dopa decarboxylase was definitively present in the human brain in amounts comparable to the amounts found in other mammals' brains and with an analogous regional distribution. Thus, finding out, and adhering to, the proper assay conditions, skillfully established by Ken Lloyd, was all that was needed to save the normal human brain from the deplorable fate of having some abnormal, rather mysterious, catecholamine synthetic pathway.

We followed up, logically, this dopa decarboxylase enzyme work by measuring the activity of tyrosine hydroxylase in the human brain (something I had tried to do while still in Vienna in 1965/1966 with Sidney Udenfriend) and demonstrated that both these dopamine synthetic enzymes were greatly reduced in the Parkinson brain.

Encouraged by this success, we proceeded to demonstrate the dopamine-replacing nature of L-dopa treatment. This we achieved by directly showing that patients treated with L-dopa had more dopamine in the striatum than untreated patients, with the highest dopamine levels shortly after the last premortem dose of L-dopa. The publication of this study, in 1975, silenced all doubts about L-dopa therapy and dopamine replacement.

A Plethora of Ideas to Test

In the course of time, we extended the work in the human brain in many directions. We studied (Ken Lloyd) the GABA receptors and the adenylyl cyclase-coupled dopamine receptors (Masato Shibuya) in the Parkinson brain; the striatal D-2 dopamine receptors in Parkinson's disease (Phil Seeman, Irene Farley, Ali Rajput) and schizophrenia (Phil Seeman, Irene Farley, Walle Tourtellotte); regional monoamine, especially brain serotonin

distribution in depression (Ken Lloyd, Irene Farley), using brains of suicide victims; and regional noradrenaline levels (Irene Farley, Kathleen Price) in brains of patients with paranoid schizophrenia. We also measured (Vladimir Hachinsky) homovanillic acid in the CSF of patients with cerebral infarction. There was also all the work in animal models, such as regional monoamine studies in rhesus monkeys on long-term neuroleptic drug therapy (George Paulson [Columbus, OH], Kathleen Price); the influence of brain dopamine mechanisms on rat EMG (Detlef Bieger); the effect of morphine (Klaus Kuschinsky) and met-enkephalin and β -endorphin (Stuart Bernie, Ken Koffer) on striatal dopamine and catalepsy; the role of corpus striatum in morphine catalepsy (Ken Koffer); the relationship between the striatum, the substantia nigra, and epileptic seizure activity (Ruggero Fariello, Masato Shibuya, Ken Lloyd); the effect of chronic neuroleptic or L-dopa administration in rats on the GABA levels in the substantia nigra (Ken Lloyd); and the selective anti-dopaminergic action (in the rat) of γ -hydroxybutyric acid (Krishna Menon, Detlef Bieger). We would sooner be short of time than of ideas to be tested experimentally.

An especially important achievement of our work in Toronto was a study of neurotransmitters, especially dopamine, in the brain of patients with Lesch-Nyhan syndrome. The results of this study provided a neurochemical reference standard for the transgenic animal model used today in studying this X-linked inherited metabolic brain disorder. This study also for the first time showed that loss of striatal dopamine was not necessarily connected with loss of nigral dopamine cell bodies—a situation later most dramatically and consequentially demonstrated by our study of a unique case of dopa-responsive (Segawa) dystonia.

Having the Best of Both Worlds: Commuting Between Vienna and Toronto (1977–Present)

In 1976/1977, I moved back to Vienna to head the Institute of Biochemical Pharmacology, newly established at the Faculty of Medicine of the University of Vienna. As is so often the case, we returned to Vienna for family reasons. We, that is my family and I, still count the 10 years we spent in Toronto as among the happiest years of our life together. The people who were so generous and hospitable, the excellent colleagues, the friendly neighbors, and the easy way to raise children all contributed to our feeling happy and very much at home in Canada. And then there was, again, the allure of nature: intense, boundless, and bountiful.

Vienna: Institute of Biochemical Pharmacology

Right from the beginning of my work in Vienna, we devoted most of our time to work with neurotoxins and with the search for mechanisms of

neurodegeneration. We studied three neurotoxins: kainic acid, ethylcholine aziridinium (AF64A), and 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP).

Kainic Acid

We started working with kainic acid when Günther Sperk (now Professor of Pharmacology at the University of Innsbruck) returned, in 1977, from his postdoctoral stay with Ross Baldessarini at the Mailman Research Center, McLean Hospital (Belmont, MA) and joined my laboratory. Soon, Michael Berger started as my Ph.D. student, joined us, and a little later Halina Baran, another of my very active Ph.D. students. Many of the studies were done in collaboration with the renowned neuropathologist Franz Seitelberger and his collaborator Hans Lassmann. Kainic acid served as a reliable excitotoxin to produce, in the rat, biochemical and morphological changes in the striatum, typical of Huntington's disease. As an epileptogenic agent, kainic acid allowed us to study the brain changes during generalized seizures and provided an especially valuable model of temporal lobe (limbic) epilepsy.

AF64A

This neurotoxin was brought to my laboratory by Heide Hörtnagl from Israel Hanin's place at the University of Pittsburgh (PA), where she had spent two years with a research fellowship. We used this agent to selectively lesion the brain cholinergic neurones, especially in the hippocampal formation. By thus imitating (in the rat) the cholinergic deficits typical of Alzheimer's disease, the analogous changes in several brain transmitter systems as well as neuropeptides could be analyzed under controlled experimental conditions. In this model, we also could clarify the role of glucocorticoids in the cholinergic degeneration in the rat hippocampus.

MPTP

MPTP was the third neurotoxin Christian Pifl and I used in connection with my continuing interest in Parkinson's disease. We did these studies in cooperation with Günther Schingnitz at Boehringer-Ingelheim's CNS pharmacology laboratory (Germany). They supplied us with brains of rhesus monkeys treated acutely or chronically with MPTP. In these studies, we established the effect of this parkinsonism-inducing dopamine neurotoxin on the regional patterns of several brain neurotransmitters (in addition to dopamine) throughout the primate brain. When Christian Pifl returned from a two-year fellowship in Marc Caron's laboratory at Duke University (Durham, NC), we continued with our interest in MPTP by studying in cell cultures the role of the specific cell membrane dopamine transporter in the phenomenon of neurodegeneration.

New Drugs for Parkinson's Disease: Back to Human Disease

An especially pleasant cooperation developed, in the 1980s, between my laboratory (Christian Pifl, Heide Hörtnagl) and Walter Kobinger and Ludwig Pichler from the pharmacology laboratory at Vienna's Ernst Boehringer Research Institute. The result of this collaboration was the introduction in the treatment of Parkinson's disease of a new class of (non-ergoline) direct dopamine agonists (i.e., B-HT 920, talipexol, in Japan; in the Western Hemisphere, the chemically closely related pramipexol).

Although my laboratory in Vienna was meant to do work exclusively in animals, this rule was broken when the neurologist Elfriede Sluga offered us valuable amyotrophic lateral sclerosis material. Susanne Malessa, Oswald Bertel, and Michael Berger used this material to study the spinal cord changes in glutamatergic, monoaminergic, and cholinergic parameters in this neurodegenerative condition.

Full-time animal work notwithstanding, my laboratory (especially Heide Hörtnagl) found time for collaborative research in patients. These studies served as a reminder for those of my collaborators doing exclusively animal work that in medical research it is, in the end, the patient that counts.

Toronto: the Human Brain Laboratory

The Birth of a New Research Facility

When I moved to Vienna, a considerable number of valuable, freshly frozen human brains that we had collected during the 10 years of my stay at the Clarke Institute remained in the Institute. Initially, work with this material was continued by Ken Lloyd. When in 1978 Ken moved to Synthelabo in Paris, I offered to Fred Lowy, the Head of the Clarke Institute at that time, to continue this work. Lowy liked the idea and I became the Head of the Clarke Institute's newly created "Human Brain Laboratory," commuting for more than 10 years between Vienna and Toronto. I divided the research work between animal experiments in Vienna and human brain work in Toronto. This enabled me to direct the easy-to-plan-ahead postmortem brain research work in Toronto, without requiring my continuous presence there. In 1980, Stephen Kish joined me from Tom Perry's laboratory in Vancouver, and soon he was able to take responsibility for the day-to-day operations of my new laboratory in the Clarke Institute.

Specific Striatal Dopamine Patterns and the Etiology of Parkinson's Disease

In the human brain laboratory we first concentrated on studying brain dopamine and other transmitters (including serotonin, noradrenaline,

GABA, glutamate, and cholinacetyl transferase) in brain disorders other than idiopathic Parkinson's disease, but accompanied by parkinsonian symptomatology. The results of these studies proved crucial when we tried to test the various hypotheses, just then put forward, postulating multiple causes of nigral cell death, thus implying a "multifactorial" etiology of Parkinson's disease. This, for us, amounted to the question: Had the striatal dopamine loss in Parkinson's disease a constant and typical pattern, or was it unpredictably variable as would be expected if multiple causative factors were involved? We carried out an elaborate inter- and subregional analysis of the dopamine patterns in the Parkinson striatum, showing that indeed Parkinson's disease had a very characteristic and constant striatal dopamine pattern. Since none of the other brain disorders with parkinsonian symptomatology mimicked the Parkinson pattern, we concluded that Parkinson's disease must have a specific etiology. By studying the striatal dopamine patterns during normal ageing, we also could disprove another idea on the possible etiology of Parkinson's disease, i.e., the "pathologically accelerated ageing of nigral dopamine neurones" hypothesis.

Beyond Parkinson's Disease

In the course of our human brain studies, we were the first, or among the first, to characterize biochemically many brain disorders other than idiopathic Parkinson's disease, among them heredity parkinsonism-dementia, neuronal intranuclear inclusion body disorders, Lesch-Nyhan syndrome, Down's syndrome, olivo-ponto-cerebellar-atrophy, fatal hyperthermia syndrome, (human) narcolepsy, progressive supranuclear palsy, dialysis encephalopathy, cortico-basal ganglionic degeneration, spinocerebellar ataxia, Huntington's disease, dementia-parkinsonism-motoneuron disease, and dystonia musculorum deformans.

To this list (that reads like a textbook of neurology) should be added a unique case (supplied by Ali Rajput) of dopa-responsive (Segawa) dystonia. Our corresponding study was the starting point for an in-depth search, including in the Clarke Institute (Yoshiaki Furukawa and Steve Kish), of the cause of this inborn (GTP cyclohydrolase I gene mutation) disorder affecting the nigrostriatal dopamine system.

Three Special Reasons for the Success of My Human Brain Laboratory

Apart from Steve Kish, who, being the right person in the right place, was gradually taking over—very successfully—my duties, a major reason for the success of my human brain laboratory had to do with another specific individual, Vivian Rakoff, Head of the Clarke Institute from 1980 to 1990. During each of my working stays at the human brain laboratory, Rakoff

regularly offered me his support, asking me if there was anything extra he could do for my laboratory. He was crucial in helping me to maintain the technical staff (Kathleen Price-Shannak and others), add laboratory space and new equipment, and make Steve Kish stay at the Clarke Institute, so as to manage our daily human brain work. Moreover, the pleasure of the countless conversations with Vivian, enjoying his brilliant gift of speech and the poetic resonance of his spoken word, made these 10 years unforgettable for me.

And then, there was the indispensable Ali Rajput, Head of Neurology at the University of Saskatchewan at Saskatoon. For more than two decades, Rajput had been systematically collecting frozen brains of patients he himself had seen and treated for prolonged periods of time; these included, in addition to Parkinson patients, many other, quite rare conditions. Rajput offered me his collaboration, including his vast experience and neurological knowledge. Without his unique brain material we would not have been able to do even one-tenth of our human brain research. Over the many years of our collaboration, Ali and I developed an ever closer relationship, both professional and—for me especially precious—personal. We continue our collaboration in Ali's neurology research laboratory in Saskatoon.

Finally, there was my own expertise which I had acquired in the many years of collecting fresh, autopsied human brains and the knowledge of how to handle and dissect them in the frozen state. Especially important was the experience I gained in identifying and isolating the various regions of the brain from 2- to 3-mm thick (frozen) slices, always cut by hand. In the beginning, Riley's unsurpassed *Atlas of the Basal Ganglia, Brain Stem and Spinal Cord* and Olszewski and Baxter's *Cytoarchitecture of the Human Brain Stem* were of great help; later, I could do without them. It was as if, with time, the human brain had started speaking to me in a language I could ever better understand. My know-how was important for our studies which crucially depended on the correct identification and reproducibility of the brain regions dissected, some of them ill-defined or without definite borders. When in the late 1970s the idea of human brain tissue banks emerged, Earl Usdin (NIMH) and Tom Chase (NINDS) asked me to host an NI Health-sponsored "International Human Brain Dissection Workshop." The workshop took place September 14–15, 1979, in Vienna and was attended by experts from all over the world. To be asked to organize this workshop was an exquisite gesture of recognition of our contributions to this field.

On Having Reached "the Top"

When, as a fledgling M.D., I started in research, nothing appeared to me more desirable than advancing to a higher position and one day reaching the top. In my youthful inexperience, I thought that this would give me

the highest degree of freedom of doing research as I pleased, without any obstacles, exclusively for myself. Later, when by good fortune I reached whatever was possible in my profession, I made a, possibly not too surprising, discovery: I realized that the opposite of what I imagined was true. When I review the beginnings of my career in research, I now see that it had been then that I had the greatest freedom, in the sense that, basically, I was responsible only for my own research, concerned with my own progress only. The higher I rose, the more of my time I had to give to the young people in the laboratory: helping them with formulating scientific concepts; teaching them (self) critical judgement; introducing them to the idea of the scientific method; trying to awaken in them the sense of wonder and reverence for nature, the object of all our inquiries; and, finally, taking responsibility for their actual research work, knowing how important it was for their future. Sometimes, all this was easy enough; sometimes, much sensibility was called for; and sometimes, a firmer guiding hand was required. All in all, the less they felt my hand, the more successful I considered my guidance. In short, in the course of my life in research, my efforts shifted from working for myself to serving others. Although to some this may appear a great pity, I think it is right: to pass on what one has received.

Arriving at the “Finishing Post”

When, in November 1991, I turned 65 and became Professor Emeritus at the University of Toronto, I could turn over to Steve Kish a well-organized, productive, widely known, and, in its way, unique research facility. Steve has since continued, at the highest level, the research tradition in my Clarke “creation,” now renamed the “Human Neurochemical Pathology Laboratory.”

In Vienna, I became Professor Emeritus in 1995, but I continued as acting Head of the Institute until February 1999. In that year, my Institute, together with the other three brain research laboratories, became part of the Institute for Brain Research, a newly founded research facility at our medical faculty—an idea I had been fighting for during the preceding 15 years. During those years, I could not avoid venturing into faculty politics. For the first time in my academic career I let myself be dragged into something like quarrels with colleagues; this happened when I tried to give the new Institute a structure that would guarantee its research as high a scientific standard as possible. Since my ideas would have meant both a change in the existing regulations on faculty structure and a shakeup within our brain research community, I suffered, not suprisingly, defeat on both fronts: “*Nec Hercules contra plures!*” The Institute opened its doors in early summer 2000. With peace and harmony long since restored, I am confident that the research done there will soon reach the goal I have envisaged for it.

People I Would Have Liked to Meet

As mentioned, I was lucky enough to meet, on my wanderings, and interact with practically everyone in my field of research and with most researchers of my generation in the other fields of neuroscience. Yet there are three individuals whom I would have liked to meet for very specific reasons.

Wilhelm Raab, a former Viennese and later Professor of Experimental Medicine at the University of Vermont at Burlington, was the first to discover, in the late 1940s, a catecholamine-like compound in the animal and human brain, with highest concentrations in the basal ganglia (caudate nucleus). Raab also was the first to inject (i.p.) D,L-dopa in order to increase the level of his new compound in the rat brain. He analyzed the caudate nucleus of 10 psychotic patients, but, unpardonably, did not think of looking at even a single Parkinson brain. I would have liked to talk to Raab, the inventive all-round experimentalist gifted with genius, to find out what kind of person he was, to hear his views on the conceiving of extraordinary ideas (of which he had so many) and on the process of discovery, and possibly also to talk with him about the bitter reality of the missed opportunities as the darker side of life as a researcher. A few months before I could visit him, Raab died in 1970 at the age of 75 "of a self-inflicted bullet wound" (*JAMA* 1970; 214: 2348).

I could have easily met the Vienna-educated Erwin Chargaff, later at the Biochemistry Department at Columbia University, at Mel Yahr's 1965 symposium at Columbia; he was a discussant of Holger Hydén's presentation. However, I missed him at the meeting. I heard him speak many years earlier in Vienna at the International Biochemistry Congress in the summer of 1958. I remember my satisfaction when Chargaff mentioned, in his opening lecture, Blaise Pascal, my favourite "thinking reed." I also remember him pondering over the fact that "with the increase in the radius of our ever expanding sphere of knowledge, also the circumference of the unknown that surrounds us, increases." I would have liked to hear Chargaff's ideas about what he thought knowledge was, how he would distinguish it from understanding, and whether amassing knowledge really led to greater understanding; I would also have questioned him about his worries and concerns about the direction in which the present-day science is moving.

I would have had little opportunity to meet Oxford's distinguished physiologist (Sir) Charles Sherrington. He died in 1952, more than four years before my time in Oxford. When reading his treatise *Man on His Nature*, I was struck most of all by the absolute honesty with which Sherrington, the scientist, posed his fundamental questions about the human condition (Sherrington, 1940). I do not think that these questions have been fully answered yet, not even by his famous pupil (Sir) John Eccles, in my opinion. I would have liked to listen to Sherrington-the-poet's musings about the

intriguing, but not too rare, association between the poetic and the scientific mind, and about his problems with the scientific mind of Goethe, the poet; hear what he thought today, against the background of his *Man on His Nature* of 1940, about the enigma of that “mindful” brain of ours, priding itself on perceiving everything there is in nature but itself being a piece of the nature perceived; and what he would have to say about the prospects and promises of the now apparently established discipline of *neurophilosophy*, as the newest and most challenging branch of our present-day neuroscience.

Looking Back

Looking back at the years I spent in research, first in Vienna and then in Toronto, and finally on both sides of the Atlantic, I am surprised to see that I have achieved everything I could have wished for. I feel happy that I so much enjoyed what I have been doing during the more than 50 years and I knew how to do. The support and recognition I received for my work, I have accepted with gratitude, as a charming reminder to do more and better. Yet the time I spent in research would, without a doubt, have meant much less to me without the friends I made during all those years; I have just recently been reminded of how many of them I do have (see, Rajput, 2001).

Coda

Apart from mentioning, here and there, my family, I have not yet said anything about my private life during the time I spent in research. The happiest part of it was, quite simply, life with my wife Christina. I married Christina in 1962. She bore me four children, a girl and three boys, each of whom I am affectionately proud of, and she has accompanied and supported me on all my wanderings and in all my endeavours for more than 40 years now. Before, however, falling into the trap of stereotypes or trivialities, I will let Robert Louis Stevenson speak for me. In his account on *An Inland Voyage*, Stevenson (1992) writes: “We asked him [Bazin, the innkeeper] how he managed in La Fère. ‘I am married’, he said, ‘and I have my pretty children . . .’ We sat in front of the door . . . Madame Bazin came out after a while; she was tired with her day’s work, I suppose; and she nestled up to her husband and laid her head upon his breast. He had his arm about her and kept gently patting her shoulder. I think Bazin was right, and he was really married. Of how few people can the same be said!”

Having come to an end with my simple and uncomplicated life’s story, what remains for me to do is give thanks—as the day is drawing to a close and the shadows lengthen—to all those mentioned in my account and the many others, although unmentioned, yet so close to the heart of my memory.

I cannot think of a better way of taking leave of you all than, as many years ago, with the lines of W. H. Auden (1991):

*Fondly I ponder You all:
without You I couldn't have managed
even my weakest of lines.*

Selected Bibliography

- Baran H, Lassmann H, Sperk G, Seitelberger F, Hornykiewicz O. Effect of mannitol treatment on brain neurotransmitter markers in kainic acid-induced epilepsy. *Neuroscience* 1987;21:679–684.
- Barolin GS, Bernheimer H, Hornykiewicz O. Side differences in brain dopamine (3-hydroxytyramine) levels in a case with hemiparkinsonism. (In German) *Schweiz Arch Neurol Neurochir Psychiatr* 1964;94:241–248.
- Berger ML, Lassmann H, Hornykiewicz O. Limbic seizures without brain damage after injection of low doses of kainic acid into the amygdala of freely moving rats. *Brain Res* 1989;489:261–272.
- Berger M, Sperk G, Hornykiewicz O. Serotonergic deafferentation partially protects rat striatum from kainic acid toxicity. *Nature* 1982;299:254–256.
- Bernheimer H, Birkmayer W, Hornykiewicz O, Jellinger K, Seitelberger F. Brain dopamine and the syndromes of Parkinson and Huntington: Clinical, morphological and neurochemical correlations. *J Neurol Sci* 1973;20:415–455.
- Birkmayer W, Hornykiewicz O. The effect of L-3,4-dihydroxyphenylalanine (= DOPA) on the Parkinsonian akinesia. (In German) *Wien Klin Wochenschr* 1961;73:787–788. (Republished in English translation in *Parkinsonism Related Disorders* 1998;4:59–60.)
- Birkmayer W, Hornykiewicz O. The effect of L-dihydroxyphenylalanine (= L-DOPA) in the Parkinsonian syndrome in man: On the pathogenesis and treatment of Parkinsonian akinesia. (In German) *Arch Psychiatr Gesamte Neurol* 1962;203:560–564.
- Bernheimer H, Hornykiewicz O. Decreased concentration of homovanillic acid in the brain of Parkinsonian patients: Result of a disturbance of central metabolism of dopamine. (In German) *Klin Wochenschr* 1965;43:711–715.
- Born GVR, Hornykiewicz O, Stafford A. The uptake of adrenaline and noradrenaline by blood platelets of the pig. *Br J Pharmacol* 1958;13:411–414.
- Ehringer H, Hornykiewicz O. Distribution of noradrenaline and dopamine (3-hydroxytyramine) in human brain: Their behaviour in extrapyramidal system diseases. (In German) *Klin Wochenschr* 1960;38:1236–1239. (Republished in English translation in *Parkinsonism Related Disorders* 1998;4:53–57).

- Farley I, Price KS, McCullough E, Deck JHN, Hordynski W, Hornykiewicz O. Norepinephrine in chronic paranoid schizophrenia: Above-normal levels in limbic forebrain. *Science* 1978;200:456–458.
- Furukawa Y, Shimadzu M, Rajput AH, Shimizu Y, Tagawa T, Mori H, Yokogochi M, Narabayashi N, Hornykiewicz O, Mizuno Y, Kish SJ. GTP-cyclohydrolase I gene mutations in hereditary progressive and dopa-responsive dystonia. *Ann Neurol* 1996;39:609–617.
- Gastager H, Hornykiewicz O, Tschabitscher H. Copper and *p*-polyphenol oxidase in the blood serum of cases with clinically manifest and sub-clinical forms of hepatolenticular disease. (In German) *Wien Zeitschr Nervenheilkd* 1954;9: 312–319.
- Hinzen D, Hornykiewicz O, Kobinger W, Pichler L, Pifl C, Schingnitz G. The dopamine autoreceptor agonist B-HT 920 stimulates denervated postsynaptic brain dopamine receptors in rodent and primate models of Parkinson's disease: A novel approach to treatment. *Eur J Pharmacol* 1986;131:75–86.
- Holzer G, Hornykiewicz O. Dopamine (hydroxytyramine) metabolism in the rat brain. (In German) *Naunyn-Schmiedeberg's Arch Exp Pathol Pharmacol* 1959;237:27–33.
- Hornykiewicz O. The action of dopamine on the arterial blood pressure of the guinea-pig. *Br J Pharmacol* 1958;13:91–94.
- Hornykiewicz O. Topography and behaviour of noradrenaline and dopamine (3-hydroxytyramine) in the substantia nigra of normal and Parkinsonian patients. (In German) *Wien Klin Wochenschr* 1963;75:309–312.
- Hornykiewicz O. Dopamine (3-hydroxytyramine) and brain function. *Pharmacol Rev* 1966a;18:925–964.
- Hornykiewicz O. Metabolism of brain dopamine in human Parkinsonism: Neurochemical and clinical aspects. In Costa E, Cote LJ, Yahr MD, eds. *Biochemistry and pharmacology of the basal ganglia*. Proc. of the 2nd Symposium of the Parkinson's Disease Information and Research Center, Columbia University, New York, 1965. Hewlett, NY:Raven Press, 1966b;171–181.
- Hornykiewicz O. Parkinson's disease: From brain homogenate to treatment. *Fed Proc* 1973;32:183–190.
- Hornykiewicz O. Psychopharmacological implications of dopamine and dopamine antagonists: A critical evaluation of current evidence. *Annu Rev Pharmacol Toxicol* 1977;17:545–559.
- Hornykiewicz O. From dopamine to Parkinson's disease: A personal research record. In Samson F, Adelman G, eds. *The neurosciences: paths of discovery, II*. New York: Birkhäuser, 1992;125–147.
- Hornykiewicz O. Levodopa in the 1960s: Starting point Vienna. In Poewe W, Lees AJ, eds. *20 years of Madopar—new avenues*. Basle: Editiones Roche, 1994;11–27.
- Hornykiewicz O. Dopamine miracle: From brain homogenate to dopamine replacement. *Movement Disorders* 2002a;17:501–508.
- Hornykiewicz O. Brain dopamine: A historical perspective. In DiChiara G, ed. *Handbook of experimental pharmacology, vol. 154/I: Dopamine in the CNS I*. Berlin: Springer-Verlag, 2002b;1–22.

- Hornykiewicz O, Kish SJ. Biochemical pathophysiology of Parkinson's disease. *Adv Neurol* 1986;45:19-34.
- Hornykiewicz O, Kish SJ, Becker LE, Farley I, Shannak K. Brain neurotransmitters in dystonia musculorum deformans. *New Engl J Med* 1986;315:347-353.
- Hornykiewicz O, Lisch HJ, Springer A. Homovanillic acid in different regions of the human brain: Attempt at localizing central dopamine fibres. *Brain Res* 1968;11:662-671.
- Hornykiewicz O, Niebauer G. The polyphenol oxidase in the human blood serum. (In German) *Arch Exp Pathol Pharmacol* 1953;218:448-456.
- Hörtlagl H, Berger ML, Havelec L, Hornykiewicz O. Role of glucocorticoids in the cholinergic degeneration in rat hippocampus induced by ethylcholine arizidinium (AF64A). *J Neurosci* 1993;13:2939-2945.
- Hörtlagl H, Berger ML, Reither H, Hornykiewicz O. Cholinergic deficit induced by ethylcholine aziridinium (AF64A) in rat hippocampus: Effect on glutamatergic systems. *Naunyn-Schmiedeberg's Arch Pharmacol* 1991;344:213-219.
- Kish SJ, Chang LJ, Mirchandani L, Shannak K, Hornykiewicz O. Progressive supranuclear palsy: Relationship between extrapyramidal disturbances, dementia, and brain neurotransmitter markers. *Ann Neurol* 1985;18:530-536.
- Kish SJ, Karlinsky H, Becker L, Gilbert J, Rebbetoy M, Chang LJ, DiStefano L, Hornykiewicz O. Down's syndrome individuals begin life with normal levels of brain cholinergic markers. *J Neurochem* 1989;52:1183-1187.
- Kish SJ, Perry TL, Hornykiewicz O. Benzodiazepine receptor binding in cerebellar cortex: Observations in olivopontocerebellar atrophy. *J Neurochem* 1984;42:466-469.
- Kish SJ, Rajput A, Gilbert J, Rozdilsky B, Chang LJ, Shannak K, Hornykiewicz O. Elevated γ -aminobutyric acid level in striatal but not extrastriatal brain regions in Parkinson's disease: Correlation with striatal dopamine loss. *Ann Neurol* 1986;20:26-31.
- Kish SJ, Shannak K, Hornykiewicz O. Uneven pattern of dopamine loss in the striatum of patients with idiopathic Parkinson's disease. Pathophysiologic and clinical implications. *New Engl J Med* 1988;318:876-880.
- Kish SJ, Shannak KS, Perry TL, Hornykiewicz O. Neuronal [^3H]benzodiazepine binding and levels of GABA, glutamate, and taurine are normal in Huntington's disease cerebellum. *J Neurochem* 1983;41:1495-1497.
- Kish SJ, Shannak K, Rajput A, Deck JHN, Hornykiewicz O. Aging produces a specific pattern of striatal dopamine loss: Implications for the etiology of idiopathic Parkinson's disease. *J Neurochem* 1992;58:642-648.
- Lee T, Seeman P, Rajput A, Farley IJ, Hornykiewicz O. Receptor basis for dopaminergic supersensitivity in Parkinson's disease. *Nature* 1978;273:59-61.
- Lee T, Seeman P, Tourtellotte WW, Farley IJ, Hornykiewicz O. Binding of ^3H -neuroleptics and ^3H -apomorphine in schizophrenic brains. *Nature* 1978;274:897-900.
- Lloyd KG, Davidson L, Hornykiewicz O. The neurochemistry of Parkinson's disease: Effect of L-dopa therapy. *J Pharmacol Exp Ther* 1975;195:453-464.
- Lloyd K, Hornykiewicz O. Occurrence and distribution of L-DOPA decarboxylase in the human brain. *Brain Res* 1970a;22:426-428.

- Lloyd K, Hornykiewicz O. Parkinson's disease: Activity of L-Dopa decarboxylase in discrete brain regions. *Science* 1970b;170:1212–1213.
- Lloyd KG, Hornykiewicz O. Occurrence and distribution of aromatic L-amino acid (L-DOPA) decarboxylase in the human brain. *J Neurochem* 1972;19:1549–1559.
- Lloyd KG, Hornykiewicz O, Davidson L, Shannak K, Farley I, Goldstein M, Shibuya M, Kelley WN, Fox IH. Biochemical evidence of dysfunction of brain neurotransmitters in the Lesch-Nyhan syndrome. *New Engl J Med* 1981;305:1106–1111.
- Pifl Ch, Hornykiewicz O, Giros B, Caron MG. Catecholamine transporters and 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine neurotoxicity: Studies comparing the cloned human noradrenaline and human dopamine transporter. *J Pharmacol Exp Ther* 1996;277:1437–1443.
- Pifl Ch, Nanoff Ch, Schingnitz G, Schütz W, Hornykiewicz O. Sensitization of dopamine-stimulated adenylyl cyclase in the striatum of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-treated rhesus monkeys and patients with idiopathic Parkinson's disease. *J Neurochem* 1992;58:1997–2004.
- Pifl Ch, Schingnitz G, Hornykiewicz O. The neurotoxin MPTP does not reproduce in the rhesus monkey the interregional pattern of striatal dopamine loss typical of human idiopathic Parkinson's disease. *Neurosci Lett* 1988;92:228–233.
- Pifl Ch, Schingnitz G, Hornykiewicz O. Effect of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine on the regional distribution of brain monoamines in the rhesus monkey. *Neuroscience* 1991;44:591–605.
- Pifl C, Zezula J, Spittler A, Kattinger A, Reither H, Caron MG, Hornykiewicz O. Antiproliferative action of dopamine and norepinephrine in neuroblastoma cells expressing the human dopamine transporter. *FASEB J* 2001;15:1607–1609.
- Rajput AH, Gibb WRG, Zhong XH, Shannak KS, Kish S, Chang LG, Hornykiewicz O. Dopa-responsive dystonia: Pathological and biochemical observations in a case. *Ann Neurol* 1994;35:396–402.
- Sperk G, Berger M, Hörtnagl H, Hornykiewicz O. Kainic acid-induced changes of serotonin and dopamine metabolism in the striatum and substantia nigra of the rat. *Eur J Pharmacol* 1981;74:279–286.
- Sperk G, Lassmann H, Baran H, Kish SJ, Seitelberger F, Hornykiewicz O. Kainic acid-induced seizures: Neurochemical and histopathological changes. *Neuroscience* 1983;10:1301–1315.
- Sperk G, Lassmann H, Baran H, Seitelberger F, Hornykiewicz O. Kainic acid-induced seizures: Dose-relationship of behavioural, neurochemical and histopathological changes. *Brain Res* 1985;338:289–295.

Literature Cited in the Text

Auden WH. A thanksgiving. In Mendelson E, ed. *Collected poems*. New York:Vintage Books-Random House Inc., 1991.

- Bertler Å, Rosengren E. Occurrence and distribution of dopamine in brain and other tissues. *Experientia* 1959a;15:10–11.
- Bertler Å, Rosengren E. On the distribution in brain of monoamines and of enzymes responsible for their formation. *Experientia* 1959b;15:382–383.
- Blaschko H. Metabolism and storage of biogenic amines. *Experientia* 1957;13:9–12.
- Cotzias GC, van Woert MH, Schiffer LM. Aromatic amino acids and modification of parkinsonism. *New Engl J Med* 1967;276:374–379.
- Dante Alighieri. *The divine comedy*, Inferno, Canto XXXIV, verses 138–139. Verse translation by Mandelbaum A. New York: Bantam Books, 1980.
- Degkwitz R, Frowein R, Kulenkampff C, Mohs U. Über die Wirkungen des L-DOPA beim Menschen und deren Beeinflussung durch Reserpin, Chlorpromazin, Iproniazid und Vitamin B6. *Klin Wochenschr* 1961;73:787–788.
- Everett GM. Evidence for dopamine as a central neuromodulator: Neurological and behavioral implications. In Barbeau A, McDowell FH, eds. *L-dopa and parkinsonism*. Philadelphia: FA Davis, 1970;364–368.
- Green G. The third man. In *The third man and the fallen idol*. London-New York: Penguin Books, 1971.
- Hertting G, Axelrod J. Fate of tritiated noradrenaline at the sympathetic nerve endings. *Nature* 1961;192:172–173.
- Holtz P, Credner K. Die enzymatische Entstehung von Oxytyramin im Organismus und die physiologische Bedeutung der Dopadecarboxylase. *Arch Exp Pathol Pharmacol* 1942;200:356–388.
- Homer. *Odyssey*, Book 4, verses 219–230. Translated by Rien EV. London-New York: Penguin Books, 1991.
- Jasper HH. Neurophysiological mechanisms in parkinsonism. In Barbeau A, McDowell FH, eds. *L-dopa and parkinsonism*. Philadelphia: FA Davis, 1970; 408–411.
- Penfield W. *The mystery of the mind*. Princeton, NJ: Princeton University Press, 1975.
- Rajput AH. Open letter to the committee on the Nobel Prize in medicine. *Parkinsonism and Related Disorders* 2001;7:149–155 (see also, *Science* 2000;291:567–569).
- Sherrington CS. *Man on his nature*. London: Cambridge University Press, 1940.
- Stevenson RL. An inland voyage. In *Travels with a donkey in the Cevennes and selected travel writings*. The World's Classics, Oxford-New York: Oxford University Press, 1992.
- Vogt M. Discussion. In Vane JR, Wolstenholme GEW, O'Connor M, eds. *Adrenergic mechanisms*. Ciba Foundation Symposium, London: Churchill, 1960;578.
- Vogt M. Functional aspects of the role of catecholamines in the central nervous system. *Br Med Bull* 1973;29:168–172.
- Ward AA. Physiological implications in the dyskinesias. In Barbeau A, McDowell FH, eds. *L-dopa and parkinsonism*. Philadelphia: FA Davis, 1970;151–159.