Basic Neurochemistry

Third Edition

Edited by
George J. Siegel, M.D.
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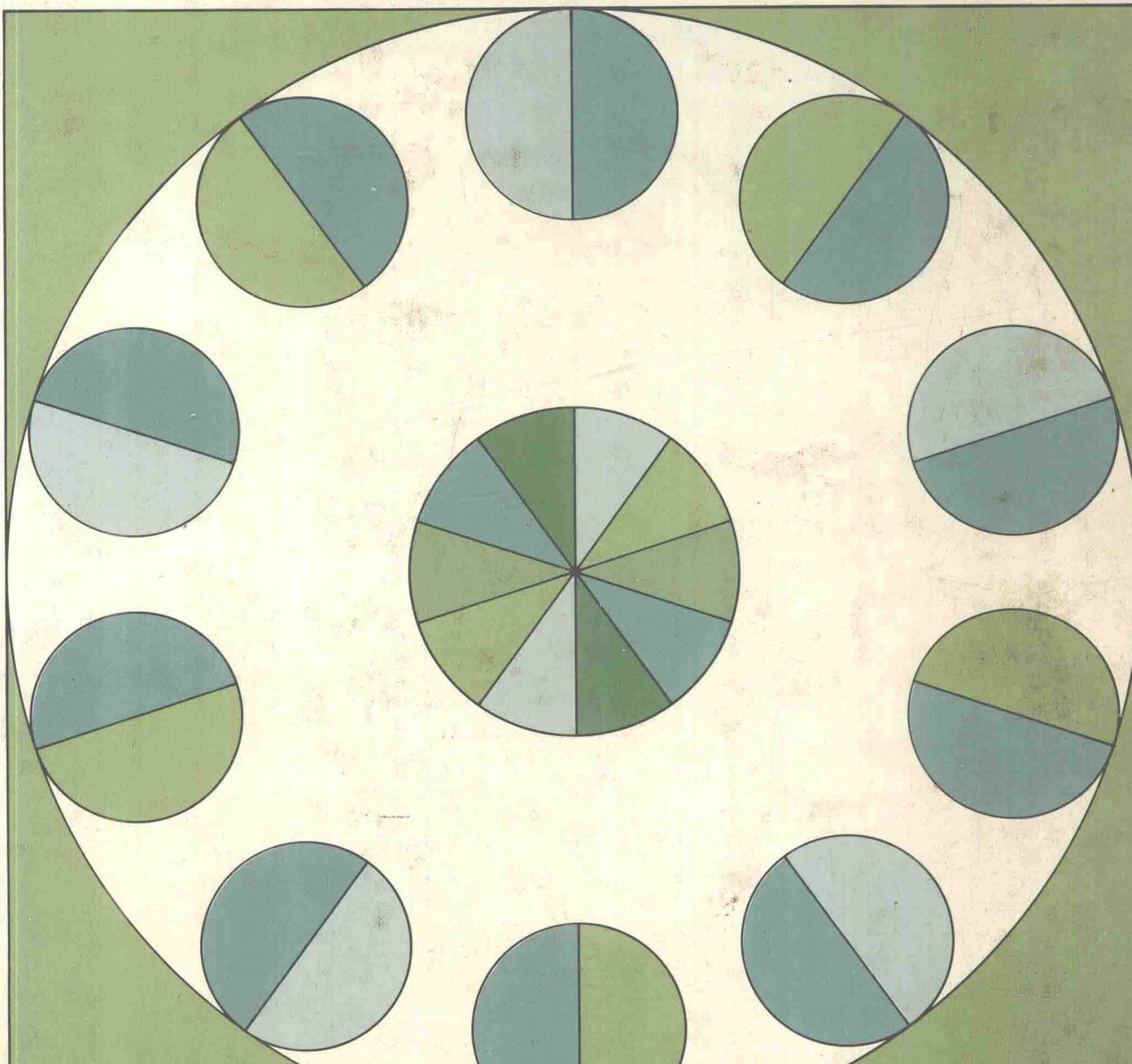
Bernard W. Agranoff, M.D.
Robert Katzman, M.D.



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EDITED BY

GEORGE J. SIEGEL, M.D.
University of Michigan Medical School,
Ann Arbor

R. WAYNE ALBERS, Ph.D.
National Institute of Neurological
and Communicative Disorders and Stroke,
Bethesda

BERNARD W. AGRANOFF, M.D.
University of Michigan Medical School,
Ann Arbor

ROBERT KATZMAN, M.D.
Albert Einstein College of Medicine
of Yeshiva University, Bronx

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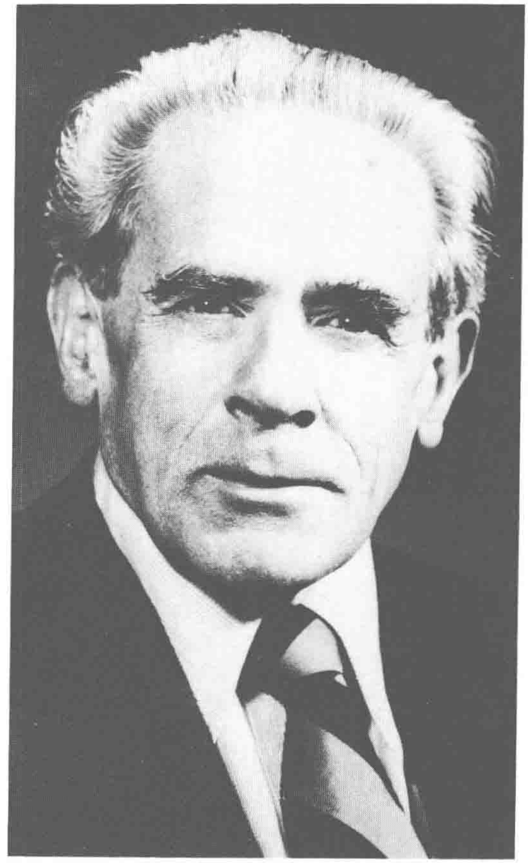
Basic Neurochemistry

Jordi Folch-Pi (1911–1979) was a major influence in the growth and development of neurochemistry. His scientific contributions involved studies on the structural components of the brain and the development of methods for their isolation and purification. He elucidated the nature of the cephalin fraction and, without access to the many sophisticated techniques available today, painstakingly determined the structure of phosphatidyl serine and of phosphoinositides. He recognized the importance of adequate methodology as a basis for conceptual progress, and his development of a simple method for the extraction of total brain lipids had a profound and lasting impact on the field of lipid biochemistry. His name is associated as well with studies on gangliosides, sulfatides, and proteolipids. He carried out pioneering studies on lipid-cation interactions and on the chemical maturation of the brain. In recent years, the proteolipids, the hydrophobic membrane proteins which he first described in 1951, became the dominant focus of his work, and he was increasingly occupied with consideration of their membrane-related functions.

In addition to his scientific contributions and international participation in decisions affecting neurochemistry, Folch was active in the formation of both the International and American societies for neurochemistry. His Catalan temperament dominated all his activities, and he pursued his love of life and the outdoors with the same intensity as his dedication to intellectual accomplishment. His colorful personality and incisive wit were loved by all.

In recognition of his wide-ranging contributions to neurochemistry and to neurochemists, the editors dedicate this volume to the memory of Jordi Folch-Pi.



Preface

In this edition there are new chapters on the history of neurochemistry (Chap. 1), synaptic transmission (Chap. 8), the opioid peptides and receptors (Chap. 13), neuropeptides (Chap. 14), cytoskeleton proteins (Chap. 20), cell adhesion molecules (Chap. 21), the molecular structure and diseases of the myoneural junction (Chap. 26), and on biochemical hypotheses of mental disorders (Chap. 38). New information and concepts concerning molecular structure and biochemical regulation have been brought into existing chapters. Notable examples include calmodulin, the calcium regulatory protein (Chaps. 3, 6, 15, and 22), the pharmacological classification of aminergic receptors (Chap. 10), amino acid transmitter systems (Chap. 12), thromboxanes (Chap. 16), the molecular composition and growth of nerve terminals and synapses (Chaps. 19, 20, and 23), and, perhaps most exciting today, the use of tracers to produce three-dimensional images of the regional metabolism of intact functioning brain (Chap. 24).

This book is intended to be comprehensive in providing students and instructors with concepts and information pertinent to nervous system and muscle biochemistry. The balance between this objective and size containment is sometimes lost to one side or the other. Many of the chapters can be studied as separate units. Some chapters, combining subjects with a common focus but from widely dispersed literature—for example, ion transport, nucleic acid and protein metabolism, brain growth and regeneration, and muscle biochemistry—are long and are best studied by the beginning reader in sections. Some subjects, such as membrane composition and receptors, myelin, and metabolism of individual classes of brain constituents, are first taken up separately and then iteratively as related to biochemical regulation, physiology, diseases, and behavior. Cross-references and the index guide the reader along these avenues. We have attempted to curtail bibliographies. Major secondary sources and key articles are marked with asterisks. Some portions of the second edition have been rearranged into other chapters in the third edition.

FROM THE PREFACE TO THE FIRST AND SECOND EDITIONS

In the past half century, neurochemistry has emerged as a distinct, if hybrid, discipline. Its unifying objective is the elucidation of biochemical phenomena that subserve activity of the nervous system or are associated with neurological diseases. For neurochemistry as for all of experimental biology, this unifying objective generates certain subsidiary goals: (1) isolation and identification of components, (2) determination of the functional interactions of the components, and (3) development of integrating hypotheses that account satisfactorily for the activities of the intact organ in terms of molecular events.

A comprehensive description of nervous system function in terms of molecular events presumably would supply intellectually satisfying and socially useful explanations of the neural responses that ultimately mediate mentation and behavior and their pathologies. Advances in neurochemistry already have led to a remarkable increase in our understanding of many of the inherited neurological disorders and to effective diagnostic techniques that may be employed both prenatally and postnatally. In another area, the identification of a deficiency in a specific neurotransmitter associated with Parkinson's disease has led to a useful therapy in this common disorder.

The validity and vitality of neurochemistry are proportionate to the successes of its practitioners in providing biochemical explanations for neural functions. These explanations cannot be derived from chemical analyses alone, and those who wish to contribute to this endeavor must be prepared to pursue various levels of structural and functional organization. The scope of neurochemistry is determined by the junctures that develop between the field of biochemistry and the fields of neurobiology, neurology, and the behavioral sciences. Neurochemists are crucially dependent upon data from these diverse subjects if they are to formulate functionally meaningful molecular hypotheses.

As a result, the student of neurochemistry must become familiar with concepts and information that are widely dispersed in the scientific literature. A number of neurochemistry courses have been organized in medical and graduate schools within recent years, and the organizers have become acutely aware of the difficulties in selecting the most significant material to place within the perspective of neurochemistry. Few existing books are at once comprehensive and sufficiently concise to be practical as texts in these courses.

A conference on neurochemistry curriculum considered these problems in June 1969 and made recommendations for the scope of the subject matter that subsequently was developed into the first edition of *Basic Neurochemistry*. It was anticipated that the experience gained through the construction and use of this text would initiate a continuing reappraisal of the field that could contribute to the evolution of later editions.

ACKNOWLEDGMENT
As with the first two editions, Helene Jordan Waddell, Director of the Rockefeller University Press, has brought to this book her outstanding knowledge of scientific writing, incisive editing, and devotion to scientific education. The editors are grateful for this continued fruitful association.

We thank Marjorie Lees for providing the biography and George Hauser for the photograph of Jordi Folch-Pi.

G.J.S.
R.W.A.
B.W.A.
R.K.

Contributing Authors

Bernard W. Agranoff, M.D.
Professor of Biological Chemistry, Neuroscience Laboratory, Mental Health Research Institute, University of Michigan Medical School, Ann Arbor
Chapter 40

R. Wayne Albers, Ph.D.
Chief, Section on Enzymes, Laboratory of Neurochemistry, National Institute of Neurological and Communicative Disorders and Stroke, Bethesda, Maryland
Chapter 3

Stanley H. Appel, M.D.
Professor and Chairman, Department of Neurology, Baylor College of Medicine, Houston
Chapter 26

Jack D. Barchas, M.D.
Nancy Friend Pritzher Professor of Psychiatry, Stanford University School of Medicine, Stanford, California
Chapter 38

Samuel H. Barondes, M.D.
Professor of Psychiatry, University of California, San Diego, School of Medicine at La Jolla, California
Chapter 21

Joyce A. Benjamins, Ph.D.
Associate Professor of Neurology, Wayne State University School of Medicine, Detroit
Chapter 23

Philip A. Berger, M.D.
Director, Stanford Mental Health Clinical Research Center, Stanford University School of Medicine, Stanford, California
Chapter 38

Murray B. Bornstein, M.D.
Professor of Neurology and Neuroscience, Albert Einstein College of Medicine of Yeshiva University, Bronx, New York
Chapter 32

Roscoe O. Brady, M.D.
Chief, Developmental and Metabolic Neurology Branch, National Institute of Neurological and Communicative Disorders and Stroke, Bethesda, Maryland
Chapter 30

M. J. Brownstein, M.D.
Laboratory of Clinical Science, National Institute of Mental Health, Bethesda, Maryland
Chapters 11 and 14

David O. Carpenter, M.D.
Director, Division of Laboratories and Research, New York State Department of Health, Empire State Plaza, Albany
Chapter 8

Donald D. Clarke, Ph.D.
Professor and Chairman, Department of Chemistry, Fordham University, New York
Chapter 17

Joseph T. Coyle, M.D.
Associate Professor of Pharmacology and Psychiatry, The Johns Hopkins University School of Medicine, Baltimore
Chapter 10

Thomas E. Duffy, Ph.D.
Associate Professor of Biochemistry in the Department of Neurology, Cornell University Medical College, New York
Chapter 35

Pierre M. Dreyfus, M.D.
Professor and Chairman, Department of Neurology, University of California, Davis, School of Medicine
Chapter 33

Stanton B. Elias, M.D.
Professor of Neurology, Baylor College of Medicine, Houston
Chapter 26

Robert A. Fishman, M.D.
Professor and Chairman, Department of Neurology, University of California, San Francisco, School of Medicine
Chapter 34

Harold Gainer, Ph.D.
Head, Section on Functional Neurochemistry, National Institute of Child Health and Human Development, Bethesda, Maryland
Chapter 14

Stanley E. Geel, Ph.D.
Adjunct Assistant Professor of Neurology, University of California, Davis, School of Medicine
Chapter 33

John Gergely, M.D., Ph.D.
Director, Department of Muscle Research, Boston Biomedical Research Institute, Boston
Chapter 27

Paul Greengard, Ph.D.
Professor of Pharmacology, Yale University School of Medicine, New Haven, Connecticut
Chapter 15

Bertil Hille, Ph.D.
Professor of Physiology and Biophysics, University of Washington School of Medicine, Seattle
Chapter 5

Jacob M. Hiller, Ph.D.
Research Assistant Professor of Medicine, New York University School of Medicine, New York
Chapter 13

Y. Edward Hsia, B.M., M.R.C.P., D.C.H.
Professor of Genetics and Pediatrics, University of Hawaii, Honolulu
Chapter 28

Robert Katzman, M.D.
Professor and Chairman, Department of Neurology and Professor of Neuroscience, Albert Einstein College of Medicine of Yeshiva University, Bronx, New York
Chapter 25

Abel L. Lajtha, Ph.D.
Research Professor of Psychiatry, New York University School of Medicine, New York
Chapter 17

Raymond J. Lasek, Ph.D.
Professor of Anatomy, Case Western Reserve University, Cleveland
Chapter 20

F. C. MacIntosh, Ph.D.
Professor of Physiology, McGill University Faculty of Medicine, Montreal, Quebec, Canada
Chapter 9

Henry R. Mahler, Ph.D.
Research Professor of Chemistry, Indiana University, Bloomington, Indiana
Chapter 19

Howard S. Maker, M.D.
Associate Professor of Neurology, Mount Sinai School of Medicine of the City University of New York, New York
Chapter 17

David B. McDougal, Jr., M.D.
Professor of Pharmacology, Washington University School of Medicine, St. Louis
Chapter 29

Bruce S. McEwen, Ph.D.
Associate Professor of Neurobiology, Rockefeller University, New York
Chapter 39

Edith G. McGeer, Ph.D.
Professor and Acting Head, Department of Neurological Sciences, University of British Columbia, Vancouver, B.C., Canada
Chapter 12

Patrick L. McGeer, M.D., Ph.D.
Professor and Head, Department of Neurological Sciences, University of British Columbia, Vancouver, B.C., Canada
Chapter 12

Guy M. McKhann, M.D.
Kennedy Professor of Neurology and Chairman, Department of Neurology, The Johns Hopkins University School of Medicine, Baltimore
Chapter 23

Pierre Morell, Ph.D.
Professor of Biochemistry, University of North Carolina School of Medicine, Chapel Hill
Chapter 32

James A. Nathanson, M.D., Ph.D.
Assistant Professor of Neurology and Affiliate in Pharmacology, Harvard Medical School, Boston
Chapter 15

Elizabeth F. Neufeld, Ph.D.
Chief, Section on Genetics and Biochemistry, National Institute of Arthritis, Metabolism and Digestive Diseases, Bethesda, Maryland
Chapter 31

William T. Norton, Ph.D.
Professor of Neurology (Neurochemistry) and of Neuroscience, Albert Einstein College of Medicine of Yeshiva University, Bronx, New York
Chapter 4

Sidney Ochs, Ph.D.
Professor of Physiology and Director of Medical Biophysics Program, University of Indiana School of Medicine, Indianapolis
Chapter 22

Fred Plum, M.D.
Professor and Chairman, Department of Neurology, Cornell University Medical College, New York
Chapter 35

Cedric S. Raine, Ph.D., D.Sc.
Professor of Pathology and Neuroscience, Albert Einstein College of Medicine of Yeshiva University, Bronx, New York
Chapters 2 and 32

Thomas S. Reese, M.D.
Head, Section on Functional Neuroanatomy, National Institute of Neurological and Communicative Disorders and Stroke, Bethesda, Maryland
Chapter 8

Fredrick J. Samaha, M.D.
Professor and Chairman, Department of Neurology, University of Cincinnati Medical Center, Cincinnati
Chapter 27

Larry J. Shapiro, M.D.
Associate Professor of Pediatrics, University of California, Los Angeles, School of Medicine
Chapter 31

Hitoshi Shichi, Ph.D.
Research Biochemist, National Institutes of Health, Bethesda, Maryland
Chapter 7

George J. Siegel, M.D.
Professor of Neurology, University of Michigan Medical School, Ann Arbor
Chapter 6

Eric J. Simon, Ph.D.
Professor of Medicine and Pharmacology, New York University School of Medicine, New York
Chapter 13

Solomon H. Snyder, M.D.
Distinguished Service Professor of Pharmacology and Psychiatry, The Johns Hopkins University School of Medicine, Baltimore
Chapter 10

Louis Sokoloff, M.D.
Chief, Laboratory of Cerebral Metabolism, National Institute of Mental Health, Bethesda, Maryland
Chapter 24

Theodore L. Sourkes, Ph.D.
Professor of Biochemistry in the Department of Psychiatry, McGill University Faculty of Medicine, Montreal, Quebec, Canada
Chapters 36 and 37

William L. Stahl, Ph.D.
Professor of Physiology and Biophysics and Medicine (Neurology), University of Washington School of Medicine, Seattle
Chapter 6

Kunihiko Suzuki, M.D.
Professor of Neurology and Neuroscience, Albert Einstein College of Medicine of Yeshiva University, Bronx, New York
Chapter 18

Phillip D. Swanson, M.D., Ph.D.
Professor and Head, Division of Neurology, Department of Medicine, University of Washington School of Medicine, Seattle
Chapter 6

Donald B. Tower, M.D., Ph.D.
Director, National Institute of Neurological and Communicative Disorders and Stroke, Bethesda, Maryland
Chapter 1

Barry Wolf, M.D., Ph.D.
Assistant Professor of Human Genetics and Pediatrics, Medical College of Virginia, Richmond
Chapter 28

Leonhard S. Wolfe, M.D., Ph.D.
Professor of Neurology and Neurosurgery and Biochemistry, McGill University Faculty of Medicine, Montreal, Quebec, Canada
Chapter 16

Basic Neurochemistry

Contents

Donald B. Tower

Chapter 1. Neurochemistry in Historical Perspective

Neurochemistry is today a mature, established discipline. It has become one of the principal neurosciences, but this is largely a post-World War II phenomenon. In fact, it is only during the last 35 years that the scientific community has come to recognize neurochemistry as a distinct discipline and that the name itself has become generally accepted. Many of us can remember when it was possible to know and keep track of virtually everything going on in the field. As neurochemistry comes to encompass a growing number and diversity of special research areas and subdisciplines, that is no longer possible.

Cornerstones of Neurochemistry

One may consider that there are four "cornerstones" upon which the development of neurochemistry rests. These are knowledge of the chemical composition of the nervous system, recognition of the metabolic bases for neural function, understanding of the chemical foundations for nerve impulse conduction and transmission, and the development of new methodologies.

FROM ALCHEMY TO CHEMISTRY: HENSING TO VAUQUELIN

Despite its relative newness, neurochemistry has its origins in work done in the eighteenth and earlier centuries [1]. The anatomy of the nervous system elucidated by Vesalius and by Willis; the circulation of the blood discovered by Harvey; and the important experiments on the physiology of muscle contraction, digestion, and respiration carried out by others [2–8] mark the beginnings of neurochemistry. The entrenched Aristotelian and Galenical doctrines of "vital" and "animal" spirits and the four "elements," or "humors," proved inadequate to account for the inherent irritability of animal tissues, for muscle contraction, and for the observations involving isolated muscle and nerve-muscle preparations made by such seventeenth- and eighteenth-century physiologists as Glisson, Swammerdam, Haller, Whytt, Galvani, and Fontana. Other studies demonstrated that digestion of foodstuffs takes place in the absence of mechanical trituration, hence indicating the role of "ferments" in the process, as reported by Sylvius, Haller, Réamur, Stevens, and Spallanzani. A number of physiological and chemical experiments by Boyle, Hooke, Lower, Hales, Priestley, and others culminated in those of Lavoisier, who showed—literally in the midst of the French Revolution—that respiration is clearly analogous to combustion and that bodily oxidations result in the production of heat, carbon dioxide, and water. Others had identified the role of blood circulation through the lungs, but it was Spallanzani who first guessed that the actual site of respiration is at the tissue level. Clearly, these eighteenth-century accomplishments anticipate the emergence of biochemistry and provide important foundations for understanding metabolism in the nervous system.

Although neurosurgeons at the French Academy of Medicine were already deriving accurate knowledge of brain functions from studies of patients with head injuries, much of chemistry still languished in alchemical notions and suffered from inevitable inadequacies in methodology. This is particularly true of the earliest studies on the chemistry of brain and nerves. Like Plato and Aristotle, early seventeenth-century observers, including Bartholin, Burrhus, Lémery, and Leeuwenhoek, speculated on the "temperament" of the brain and its fatty nature, which they compared to spermaceti (a waxlike substance derived from whale oil) [1]. Prominent chemists of the time, such as Lémery, subjected body fluids and tissues, including brain, to the standard alchemical procedures of distillation, digestion, rectification, and calcination to obtain new and better medicinal remedies. However, the first detailed account of chemical analysis of brain tissue and the first report of the isolation of a specific brain substance (phosphorus) are given by the obscure Hessian physician Johann Thomas Hensing (1683–1726) in his monograph *Cerebri examen chemicum ex eodemque phosphorus singularem omnia inflammabilia accendentem*, published at Giessen in 1719 [1].

As one might expect, Hensing's approach was to examine the brain's nature *per ignem* (with fire, which was then the chemist's most powerful tool). According to Hensing, upon heating, beef brain yielded (in order of appearance) a very subtle "water," termed "spirituous"; a volatile, acrid "oil"; a "fixed salt" containing most of the "fixed water," or spirit; and finally, dry "earth" (the *caput mortuum* of the alchemist). He carefully described the isolation and identification of elemental phosphorus from 12 ounces of beef brain and likened it to phosphorus isolated earlier from urine and feces by Brand, Kunckel, and Homberg, and from minerals by Balduin. This was the "*phosphor mirabilis*" examined in detail by Robert Boyle in his 1680 treatise on noctilucence. Hensing, in discussing his own results, suggested that the various substances found in brain were somehow combined and wondered whether the phosphorus could be involved in the functioning of the "animal spirits" that were thought to originate in the brain [1, 9].

Historically, Hensing's work was little more than a curiosity. It had little impact on subsequent studies, although it was cited by Thouret, Sömmering, J. F. John, and Thudichum. During the next century, several inorganic and simple organic substances were isolated from brain, and Hamburger reported that on drying gray and white matter, about 81 percent and 69 percent, respectively, are volatilized. However, it was the analyses of Fourcroy (1793) and of his pupil Vauquelin (1811) that marked the beginnings of modern compositional studies that would culminate in Thudichum's monumental work some fifty years later. Thus, Nicolas-Louis Vauquelin (1763–1829) found human brain to contain 80 percent water; 7 percent "albumen"; about 5 percent fatty materials (clearly distinct from ordinary fats and oils and from the spermaceti and soaps proposed by earlier investigators); "osmazomes" (equivalent to a meat extract); and salts (including phosphates of potash, lime, and magnesia, and common salt and sulfur) accounting for almost 8 percent. The present-day equivalents would be 77.0, 8.05, 11.0, and 3.95 percent, respectively. Except for his lipid analyses, which are low because at that time only alcohol was used as extractant, Vauquelin's data approximate those of Thudichum and present-day investigators [10].

Vauquelin, justifiably one of the leading scientists of his era, succeeded to the chair of chemistry at the Paris Faculté de Médecine in 1809. His teacher Fourcroy, a leading revolutionary, was successor to Lavoisier and a councillor of state under Napoleon. Although not politically involved, Vauquelin served the government in many important capacities. His intimate friends included Lavoisier, Berthollet, De Morveau, Gay-Lussac, Chevreul, and many others. He discovered several chemical elements and a number of organic compounds, including the first amino acid, asparagine. It is not surprising that his "Analyse de la matière cérébrale de l'homme et de quelques animaux" (*Annales de la Muséum d'histoire naturelle*, Vol. 18, pp. 212–239, 1811) had a prompt and widespread impact. The monograph was reprinted in leading French, German, and English scientific periodicals and served as a basis for most subsequent studies on brain chemistry. It is of interest that French chemistry flourished in the social and political turbulence of the Revolution and the First Empire.

FROM COMPOSITION TO METABOLISM: THUDICHUM TO WINTERSTEIN

During the latter part of the eighteenth century and the beginning of the nineteenth, neurophysiology prospered and came to occupy the central role in studies of the nervous system [2, 4, 5, 8, 11, 12].