A HISTORY OF NERVE FUNCTIONS

Recent developments have extended our knowledge of the basic functions of nerves – notably, demonstration of the mechanism within nerve fibers that transports a wide range of essential materials. To understand how this discovery occurred, it is necessary to examine its history. The story begins in ancient Greece when nerves were conceived of as channels through which animal spirits carried sensory impressions to the brain. As science developed, the discoveries of various physical and chemical agents supplanted the agency of animal spirits until the molecular machinery of transport was recognized. In this fascinating and complete history, Sidney Ochs begins with a chronological look at this path of discovery, followed in the second half by a thematic approach, wherein the author describes the electrical nature of the nerve impulse, fiber form, and its changes in degeneration and regeneration, reflexes, learning, memory, and other higher functions in which transport participates. *A History of Nerve Functions* will serve as an invaluable resource for historians of neuroscience and medicine, philosophers of science and medicine, as well as for neuroscientists.

Sidney Ochs is Professor Emeritus of Cellular and Integrative Physiology at the University of Indiana School of Medicine. He has been a pioneer in research in the field of axoplasmic transport in nerves, publishing the first monograph on the subject. He has contributed more than 300 publications on various aspects of the peripheral and central nervous systems, including a textbook on neurophysiology. He founded the *Journal of Neurobiology* and was a Regional Organizer in the establishment of the Society for Neuroscience, as well as later acting as a Councilor of the Society.

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From Animal Spirits to Molecular Mechanisms

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PREFACE

Within the last half of the twentieth century, two fundamental properties of nerve were established: in midcentury, the ionic nature of the propagated action potential; and, later in the century, the process in the fibers known as *axonal flow, axoplasmic transport, axonal transport, neuroplasmic transport*, and so on. By means of the transport mechanism, essential components synthesized in the nerve cell bodies are carried out within the relatively long length of nerve fibers to maintain their viability and function. Components transported include the ion channels and ion pumps needed to maintain membrane potentials all along the length of the fibers, metabolic and structural components supporting the form and viability of the fibers, and substances providing for reception at sensory terminals and neurotransmitters at motor terminals. This is indeed a protean mechanism, fundamental for an understanding of modern neuroscience and a rational basis for interpretation of neuropathies and eventually their therapy.

Although the discovery of the properties and molecular nature of the transport mechanism and related topics is a major theme, this account is not restricted to the last half century. The concept can be traced back to its earliest beginnings in the sixth and fifth centuries B.C., respectively, when philosophy and science had their origins in ancient Greece. Nerves were then conceived of as channels carrying sensory impressions by animal spirits to the brain where consciousness awareness and reasoned judgment were located, and from it willed commands were carried by nerves to actuate the muscles. (Notable exceptions to the concept that the brain played this role were Aristotle and the Stoics, who viewed the heart as serving those higher functions.) From ancient Greece, as step-by-step physiological and anatomical sciences evolved and new physical principles and chemical substances were discovered over the centuries, various agents were proposed to replace animal spirits without prevailing, until, in the nineteenth century, the electrical nature of the nerve impulse was established and, later in the century, the elementary unit of the nervous system, the neuron, was recognized.

In the last half of the twentieth century, electron microscopy revealed the fine structure of the nerve fiber and isotope tracers, and biochemical techniques were used to characterize the movement of proteins and other materials in them and reveal the molecular nature of the transport mechanism. The same processes discovered in peripheral nerves were also found to take place in the neurons of the central nervous system, where transport in the brain was seen as underlying neuronal changes related to higher behavior, to learning and memory. Thus, a close connection can be traced from the earliest conceptions of nerve as a channel for an agency responsible for sensation carried to and motor responses from to the brain.

Whereas this history makes a case for the similarity of the earliest concept of nerve to its present understanding, a Whiggish view of history, the interpretation that the past simply evolves in a direct progressive path to the present is not taken. Our story includes false steps, strong personal oppositions, and periods of stagnation or even regression, these setbacks overcome with new thinking, often provided by the importation of concepts and techniques from other sciences. Some account of the cultural background out of which the science developed has been touched on, where philosophical and religious teachings have acted to further or hinder the progress of discovery. Liberal use was made of the best available scholarship to give English translations of some of the primary sources to convey what was thought at the time. This, it is hoped, will help avoid anachronisms, the temptation to judge the work of our predecessors on the basis of present information and standards. I have retained the older phraseology; and for some obsolete words, I have supplied present-day equivalents in square brackets. Square brackets were also used where elisions or additions were made to further the sense of a quoted passage.

A chronological order has in general been followed for the first six chapters until, by the late eighteenth century, the known properties of nerve and the nervous system had grown to the point that keeping to a strict chronological order became cumbersome. From the seventh chapter on, a thematic course was followed, with some aspects of the subject carried forward to our day; the electrical nature of the nerve impulse, the form of the nerve fiber, its degeneration and regeneration, the characteristics and molecular mechanisms proposed for axonal transport, agents interfering with transport and their relationship to neuropathology, reflex responses, the relationship of brain structures and transport to higher behavior, to learning and memory. Some implications of those latter subjects are dealt with in a more speculative manner in the last chapter, as part of the postscript.

Rather than an attempt to chronicle all aspects of nerve, the main purpose is to give an account of those concepts thought to be most essential that are related to transport. Even so, the large and ever-increasing body of literature has made the problem of selection, particularly in dealing with the more recent literature, acute. I am only too aware that, to keep within the bounds of a single volume, some aspects and worthwhile contributions could not be included. My hope is that omissions in this respect may be overcome by recourse to the copious references supplied.

Although, as far as is known to me, this is the first book-length treatment of the history of nerve in which axonal transport figures in a major way, some recent histories of neuroscience have dealt with some aspects of transport or related topics. Clarke and O'Malley have given translations of a number of important historical writings on nerve, brain, and spinal cord.[1] The book by Clarke and Jacyna, dealing with fundamental developments in the history of the nervous system during the first half of the nineteenth century, contains important sections relative to transport.[2] Liddell discusses the early microscopic studies of the nerve fiber.[3] Some of the earlier history of transport was briefly touched on in my book, which gives a general exposition of axoplasmic transport up to 1982.[4] Spillane's book on nerve has a more extensive clinical orientation.[5] The histories of neuroscience by Brazier[6] and those by Finger[7] provide useful background information. These deal for the most part with the central nervous system. Important reviews dealing directly with portions of the history of transport have been given by Clarke,[8] Rothschuh,[9] and Billings[10] and in collected volumes on axoplasmic transport.[11]

The writing of this book was shaped by studies of peripheral nerve, spinal cord, and brain properties carried out over a period of more than 50 years. My interactions in those studies with colleagues, post-doctoral fellows, and students was not limited to only the investigative work at hand, but they acted as a stimulus to further understand the historical basis of what we were involved with. I give my heartfelt thanks to all who shared their studies with me. I would like to express my gratitude to Ralph Waldo Gerard who took me on as a doctoral student at the University of Chicago, and to Anthonie van Harreveld, with whom I served as a post-doctoral Fellow at the California Institute of Technology, who treated me as a colleague and friend. Thanks must also go to the librarians at the Ruth Lilly Library of the Indiana University School of Medicine who have been unfailing in their help with difficult to obtain materials. I wish to express my thanks to Dr. Katrina Halliday, my editor at Cambridge University Press, for her support and to those other editors at Cambridge who through the years did not lose faith that this book would eventuate. Last, but not least, this book would not have been possible without the support of my wife Bess and our children Rachel, Raymond, and Susie who each in their own way has helped in the course of making this book.

[1] (Clarke and O'Malley, 1968). [2] (Clarke and Jacyna, 1987).
[3] (Liddell, 1960). [4] (Ochs, 1982). [5] (Spillane, 1981).
[6] (Brazier, 1984) and (Brazier, 1988). [7] (Finger, 1994) and (Finger, 2000).
[8] (Clarke, 1968) and (Clarke, 1978). [9] (Rothschuh, 1958). [10] (Billings, 1971).
[11] (Weiss, 1982), and (Iqbal, 1986).