HANDBOOK OF PHYSIOLOGY

A critical, comprehensive presentation

of physiological knowledge and concepts

SECTION 1:

Neurophysiology

VOLUME I

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Foreword

The original literature in the field of physiology has become so vast and is growing so rapidly that the retrieval, correlation and evaluation of knowledge has become with each passing year a more complex and pressing problem. Compounding the difficulties has been the inevitable trend toward fragmentation into smaller and smaller compartments, both of knowledge and of research skills. This trend is not only inevitable, but it is necessary to healthy growth. It must, however, be accompanied by the development of mechanisms for convenient and reliable re-integration in order that knowledge shall not be lost and research effort wasted.

The American Physiological Society has enlisted the cooperation of physiological scientists over the world in attempting to provide a mechanism in this *Handbook of Physiology* series for providing a comprehensive but critical presentation of the state of knowledge in the various fields of functional biology. It is intended to cover the physiological sciences in their entirety once in about ten years, and to repeat the process periodically thereafter.

Preface

This *Handbook of Physiology*, like its predecessors from von Haller on, is designed to constitute a repository for the body of present physiological knowledge, systematically organized and presented. It is addressed primarily to professional physiologists and advanced students in physiology and related fields. Its purpose is to enable such readers, by perusal of any Section, to obtain a working grasp of the concepts of that field and of their experimental background sufficient for initial planning of research projects or preparation for teaching.

To accomplish this purpose the editors have planned a book which would differ from textbooks in being more complete, more analytical and more authoritative. It would differ from a series of monographs in being organized on a consistent plan without important gaps between topics and with as nearly as possible the same relation of intensity of coverage to importance of topic throughout. It would differ from publications emphasizing new developments in that the background of currently accepted or classical concepts would be set forth, newer ideas receiving not more than their due proportion of emphasis relative to the whole body of knowledge in the field. Finally it would differ from a collection of original papers on a series of topics in that it would provide an integrated condensation and evaluation of the material contained therein. Moreover, the overall plan provides that the key experimental findings in the development of each field of investigation be described and discussed in sufficient detail (with appropriate illustrations, quantitative data and adequate documentation) to make clear their nature, validity and significance for the fundamental concepts of the field. The success of this endeavor must be left to the reader's judgment.

This *Handbook* stands as the current representative of an historic series of efforts to collect and systematize biological knowledge—a series continued when the Board of Publication Trustees of the American Physiological Society decided in 1953 to sponsor the present undertaking. A brief list of notable predecessors may interest some readers. First known of the series is a brief Sumerian 'pharmacopeia' dating from perhaps 2100 B.C. Later examples included several Egyptian papyri such as the *Ebers* and the *Edwin Smith.* Far more extensive compilations characterized the Greco-Roman period. Outstanding among those were the Hippocratic collection (written by several authors) and the encyclopedic writings associated with the names of Aristotle, Theophrastus, Celsus and Galen (Pliny's work is useful chiefly to the student of folklore). These treatises systematized knowledge of the day over a wide range and set forth new information based on the authors' observations. Thus they combined the roles of handbook and scientific journal, a pattern that persisted until development of scientific journals (in the seventeenth century). Other important compilations were made by the writers of the 'Moslem Renaissance' such as Rhazes and Avicenna, to whom much of the Greco-Roman literature was available.

European biological compendia of the Christian era, from the fourth century *Physiologus* to the extensive biological encyclopedias of the sixteenth and seventeenth centuries, differed greatly in character from Greco-Roman and 'Moslem Renaissance' work. Marked by strong theological and anthropocentric orientation, they lacked the descriptive accuracy and rational approach of the ancients. *Scientia* was considered ancillary to *sapientia.* Nature was studied chiefly to obtain illustrations for moral tales and religious dogmas, not to gain knowledge or insight, or to learn how to manipulate and control the environment. Writers showed little critical capacity and failed to distinguish between the true and the fabulous, the important and the trivial. These elements are still evident in such major sixteenth century biological encyclopedias as Gesner's *Historiae Animalium* (5 volumes, 1551–1587), and Aldrovandi's *Opera Omnia* (13 volumes, 1599–1677). In both the mark of the medieval *Bestiary* is strong.

However, the tide was turning in the sixteenth century despite these notable examples of medieval *Weltanschauung*. The range and precision of anatomical knowledge were greatly extended by publication in 1543 of Vesalius' *De Humani Corporis Fabrica*. It is interesting to note that increasingly accurate handbooks of descriptive botany began to appear. At about this time the great transition from the medieval to the modern outlook (the 'scientific revolution of 1500–1800') was under way. This has been succinctly described by Raven: "Little by little, nonsense was recognized, fables were exploded, superstitions were unmasked and the world outlook built up out of these elements fell to pieces. The seemingly irrelevant labors of men like Turner or Penny to identify and name and describe bore fruit in a refusal to accept tradition on authority and in an insistence that statements must be based upon observation and capable of verification" (C. E. Raven. *English Naturalists from Neckam to Ray*. 1947, p. 227).

The rise of the mechanical philosophy in the seventeenth century and the rationalism of the eighteenth furnished an intellectual climate favorable for science. This was reflected in the papers, monographs and compendia produced. In the spirit of the time, Diderot, d'Alembert and their associates prepared the *Encyclopédie ou Dictionnaire Raisonné Des Sciences, Des Arts et Des Métiers* (35 volumes, Paris, 1751–1780). While the major contribution of this influential work was to diffuse the rationalist interpretation of the universe in mechanistic terms, it included many contributions in the biological sciences. Together these constitute a transitional stage of biological handbook —quite modern in spirit but not in respect of fact or concept.

While the *Encyclopédie* was in preparation in Paris, the Swiss savant Albrecht von Haller was compiling the *Elementa Physiologiae Corporis Humani* (8 volumes, Lausanne, 1757–1765). This comprised both a handbook of anatomy and physiology and a vehicle for publication of much original work by the author. Compared to earlier work the writing shows impressive critical capacity, detailed familiarity with the achievements of others, ability to distinguish the trivial and the important and over-all scientific insight. This was the first of the great series of German *Handbuch* of physiology.

The vast increase in scientific activity, with multiplication of investigators, laboratories and journals, that characterized the nineteenth century led to more frequent collection and systematization of knowledge in the several active fields. This was naturally centered in Germany where scientific activity was greatest. Notable examples of handbooks of physiology were R. Wagner's *Handwörterbuch der Physiologie mit Ruchsicht auf Physiologisches Pathologie* (Braunschweig, 1842–1853); L. Hermann's *Handbuch der Physiologie* (Leipzig, 1879–1883); C. Richet's unfinished *Dictionnaire de Physiologie* (Paris, 1895–1928); E. A. Schäfer's *Text-Book of Physiology* (Edinburgh and London, 1898–1900); W. Nagel's *Handbuch der Physiologie des Menschen* (Leipzig, 1905–1910); the massive *Handbuch der Normalen und Pathologischen Physiologie, mit Berücksichtigung der Experimentellen Pharmakologie*, edited by A. Bethe, G. von Bergmann, G. Embden and A. Ellinger (Berlin, 1926–1932); and our immediate predecessor, G.-H. Roger and L. Biñet's *Traité de Physiologie Normale et Pathologique* (Paris, 1933–1940). Characteristically these handbooks comprised the contributions of many authors and, in the last two, collaboration of several editors as well. These, with comparable compilations in cognate fields such as K. von Bardeleben's *Handbuch der Anatomie des Menschen* (Jena, 1896–1911) and E. Abderhalden's *Handbuch der Biologischen Arbeitsmethoden* (Berlin, 1925–1939), have provided a corpus of collected and systematized scientific knowledge. A notable feature of all handbooks, including the present one, is their increasingly international character, reflecting the broadening base of the world of science.

Survey of these codifications from the earliest on provides a basis for Abraham Flexner's trenchant comment on the history of medicine. "From the earliest times medicine has been a curious blend of superstition, empiricism, and that kind of sagacious observation which is the stuff out of which ultimately science is made. Of these three strands—superstition, empiricism and observation—medicine was constituted in the days of the priest-physicians of Egypt and Babylonia; of the same three strands it is still composed. The proportions have, however, varied significantly; an increasingly alert and determined effort, running through the ages, has endeavored to expell superstition, to narrow the range of empiricism and to enlarge, refine and systematize the scope of observation. . . . The general trend of medicine has been away from magic and empiricism and in the direction of rationality and definiteness" (A. Flexner. *Medical Education. A Comparative Study.* New York, 1925). We trust that continuation of this trend is reflected in this *Handbook.*

It is difficult to acknowledge properly the devoted and effective work which has made this vast undertaking possible. Its success is due alike to the contributors, to the editorial staff and to the Board of Publication Trustees of the American Physiological Society. Alike to all of these is due the gratitude of the world of physiologists for a task well done.

JOHN FIELD

Editor-in-Chief, 1954–1958

Preface to the Section on Neurophysiology

As the Editor-in-Chief has pointed out, the decision of the American Physiological Society to sponsor a *Handbook of Physiology* continues an historic series of efforts to collect and systematize knowledge in more readily available forms. Although sharing many of the features of its predecessors, the present *Handbook of Physiology* is likely to be less formidable than most of them. Its goal, like that of chariot racing, has been to secure a balanced perch astride the rushing progress of investigative advance. It attempts to survey the status of physiology just past the mid-mark of the twentieth century. In the case of each topic, the compilative accumulation of analytic data is either introduced or concluded by synthesizing comments of an 'elder statesman' still active in the field. Thus a balance is sought between the presentation of specific information and conceptualization appropriate to it.

Appropriately also, the *Handbook* begins with consideration of the nervous system by which the activities of other portions of the body are coordinated and controlled. The nervous system remains the last organ of the body still formidably to resist investigative attack; many fundamental concepts of its function lie waiting in the future. Views proposing a spiritual basis for neural function have obtained since classical antiquity. Only in the past century have materialistic outlooks been effectively introduced, first with respect to the nerve impulse, then in reflex function and, most recently, in Russian views applying concepts of reflex physiology to an understanding of higher activities of the brain. In this latter area, however, subjective experience and the mind still receive major attention in the West from the disciplines of psychology and psychiatry, a testimony to continuing dualistic points of view regarding function of the neural organ. In contemporary studies of physiological psychology the gap between brain and mind seems most rapidly to be closing; prominent representation of this field is probably the most novel feature of the table of contents of the present Neurophysiology Section.

More than customarily, appreciation should be expressed to the contributing authors of this *Handbook*. Each has been willing to add to the many energy-draining burdens of a busy career the difficult task of surveying a field of investigative specialty both for the benefit of associates and for the general welfare of physiological science. The remarkably fine series of articles testifies to the generosity and skill of each contributor. It is to be hoped that reader appreciation may compensate these authors.

Special gratitude should be expressed also for the efforts of the Executive Editor, Victor Hall. His background of editorial experience with the *Annual Review of Physiology* enabled the manifold labors of this 'sweet-blooded' man to be performed so deftly as perhaps to escape the attention of the general reader.

Hopefully, all who use this *Handbook* will wish as I do to thank, if only silently, the contributing authors and the Executive Editor for their generous efforts and to applaud them for such a fine accomplishment.

H. W. MAGOUN

Section Editor

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CHAPTER I

The historical development of neurophysiology

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CHAPTER CONTENTS

EARLY CONCEPTS OF NERVOUS ACTIVITY

IN CONTRAST TO MEDICINE, a science demanding synthesis of observations, experimental physiology, with its reliance on analysis and laboratory work, has little significant history before 1600. Leaders in medicine developed and practiced its therapies for many centuries before they felt the need to understand the nature and functions of the body's parts in any truly physiological sense and, when the urge for this knowledge first arose, it was to come as much from the philosophers as from the healers of the sick.

Neurophysiology (a term not to come into use until centuries later) had as a legacy from the ancients only their speculative inferences and their primitive neuroanatomy. Aristotle had confounded nerves with tendons and ligaments, had thought the brain bloodless and the heart supreme, not only as a source of the nerves but as the seat of the soul. Herophilos and Erisistratos had recognized the brain as the center of the nervous system and the nerves as concerned both with sensation and movement. However, preliminary to all disciplines was the development of the scientific method and in this Aristotle was a forerunner. If Aristotle is to be evaluated as a scientist, it must be admitted that he was almost always wrong in every inference he made from his vast collections of natural history and numerous dissections; yet in spite of the stultifying effect of the immoderate worship given him by generations to follow, he stands out as a pioneer in the background of every scientific discipline. He owes this position to his invention of a formal logic, and although his system lacked what the modern scientist uses most, namely hypothesis and induction, his was a first step towards the introduction of logic as a tool for the scientist. Unfortunately Aristotle did not use his logic for this purpose himself.[1] As Francis Bacon put it, Aristotle "did not consult experience in order to make right propositions and axioms, but when he had settled his system to his will, he twisted experience round, and made her bend to his system."

In the second century A.D., Galen's experimental work added little to establish the functions of the animal structures he dissected, though the hypotheses he suggested were put forward so authoritatively that they remained unchallenged for nearly 1500 years. To the intervening centuries, dominated as they were by the Christian church, the teleology implicit in Galen's approach was attractive. Early Western acquaintance with his writings depended entirely upon Latin translations of Arabic. It was only after the fall of the Byzantine Empire and the expulsion of the Greek monks from the area of Turkish conquest that the Greek language began to be read at

[1] The fragments of Aristotle's writings that exist (probably his lecture notes) were not collected until more than 200 years after his death. His *Opera* were among the early scientific works to be printed (in Latin, 1472), nearly 1800 years after his death. English translations (*The Works of Aristotle*) were published by the Clarendon Press, Oxford, in several volumes between 1909 and 1931, edited by J. A. Smith and W. A. Ross.

all generally by scholars in Western Europe (1, 2). In the sixteenth century Thomas Linacre (3), physician to Henry VIII, who had taught Greek to Erasmus at Oxford, translated some of Galen's works into Latin directly from the Greek. The copies he gave to Henry VIII and to Cardinal Wolsey can be seen in the British Museum. Erasmus, commenting on Linacre's translations, said, "I present you with the works of Galen, by the help of Linacre, speaking better Latin than ever they spoke Greek."

Galen's emphasis, in spite of his dissection of animals, was not so much on the structures he found as on the contents of the cavities within them. Function, according to his doctrine, was mediated by humors which were responsible for all sensation, movement, desires and thought, and hence pathology was founded on humoral disturbance. The role of the organs of the body was to manufacture and process these humors. His teaching about the nervous system was that the blood, manufactured in the liver and carrying in it natural spirits, flowed to the heart where a change took place converting them into vital spirits. These travelled to the *rete mirabile* (the terminal branches of the carotid arteries at the base of the brain) where they were changed into animal spirits,[2] a subtle fluid which then flowed out to the body through hollow nerves. Some of these ideas Galen developed from those of his predecessors (such as Alcmaeon, Herophilos, Erisistratos), some were inspired by his dissection of animals, but all were hypothetical, none had any experimental proof or even partial support, yet some of them were to last well into the nineteenth century.

The sixteenth century gave to physiology its first textbook.[3] This was the contribution of Jean Fernel, physician and scholar, who in 1542 published his *De Naturali Parte Medicinae* (4). This was so well received that it saw many editions. In the ninth of these Fernel changed the title to *Medicina* (5) and named the first section of the revised book *Physiologia.* According to Sherrington (6) this was the first use of the term 'physiology.' There is, however, a manuscript in the Danish Royal Library entitled *Physiologus* that deals with animals and monsters. This copy is an Icelandic version of an apparently much-copied treatise; it is a kind of bestiary. For some time after Fernel's revival of it, the term 'physiology' was still used by most writers to mean natural philosophy. An example of this usage is to be found in the full title of Gilberd's book on the magnet published in 1600. Although still grounded in a classification derived from the four elements of the ancients, Fernel's physiology nevertheless shows dawning recognition of some of the automatic movements which we now know to be reflexly initiated for, although only the voluntary muscles were known to him, he realized that sometimes they moved independently of the will.

Before the seventeenth century opened, a technical achievement in another field laid a foundation on which physiology was to spread. Lagging about 50 years after the invention of printing came the development of copper plate engraving and accurate reproductions of anatomists' drawings became more widely distributed. Supreme, however, among the woodcuts contemporary with the early engravings were those made from the drawings of Jan Stephen of Calcar for the anatomical studies of Vesalius (7–9). These, published in 1543, were to draw the praise of John Evelyn in his treatise on chalcography.[4] After

1. GALEN (130–200 A.D.). *Opera Omnia* (*in aedibus Aldi et Andrea Asulani*) (in Greek). Venice, 1525. 5 vol.
2. GALEN. *Opera Omnia* (in Greek). Basle, 1538.
3. GALEN. *De Facultatibus naturalibus*, Latin translation by Thomas Linacre. London: Pynson, 1523; English translation by A. J. Brock, Loeb Classical Library. London: Heineman, 1916.

[2] The usage of the term 'animal spirits' throughout the centuries carries the connotation of the Latin *anima* meaning soul and has no reference to the modern meaning of the word 'animal.'

[3] No other was to appear until the beginning of the eighteenth century when Johann Gottfried von Berger (1659–1736) published his textbook entitled *Physiologa Medica sive natura humana*. Wittenberg: Kreusig, 1701.

[4] "Nor lesse Worthy of Commendation are the Gravings. . . those eleven pieces of Anatomie made for Andrea Vessalius design'd by Calcare the Fleming, an Excellent painter, and which were afterwards engraven in Copper by Valverdi in little." Evelyn, John. *Sculptura: or the History, and Art of Chalcography*. London, 1662. The reference is to the plagiarism of the Spaniard, Juan Valverde. *Vivae Imagines Partium Corporis Humani*. Antwerp: Plantin, 1566. (His artist was Becerra.)

4. FERNEL, JEAN (1497–1558). *De Naturali Parte Medicinae*. Paris: Simon de Colines, 1542.
5. FERNEL, J. *Medicina*. Paris: Wechsel, 1554. *Physiologia*, translated into French by Charles de Saint Germain, *Les VII Livres de la Physiologie, composés en Latin par Messire Jean Fernel*. Paris: Guignard, 1655.
6. SHERRINGTON, C. S. *The Endeavour of Jean Fernel*. Cambridge: Cambridge, 1946.
7. VESALIUS, ANDREAS (1514–1564). *De Humani Corporis Fabrica*. Basle: Oporinus, 1543; translated into English by J. B. de C. M. Saunders and C. D. O'Malley. New York: Schuman, 1947.
8. VESALIUS, A. *Epitome*. Basle: Oporinus, translated into English by L. R. Rind. New York: Macmillan, 1949.
9. VESALIUS, A. *Tabulae Sex*. Venice, 1538.

centuries in which human dissection could only be done relatively furtively, a more liberal view had grown up in Italy and among a number of contemporary anatomists, Vesalius is pre-eminent. In themselves, however, with the exception of an experiment showing that the nerve sheath is not vital for conduction, his studies made no contribution to the dynamics of function. Although an opponent of Galen and an exposer of his anatomical errors, Vesalius had no more satisfactory concept of nervous activity to offer than that of animal spirits flowing from the brain down pipe-like nerves to the muscles. Yet for the study of the nervous system, as for other branches of physiology, the publication of *De Humani Corporis Fabrica* is the outstanding contribution of the sixteenth century, the earlier chalk drawings of Leonardo Da Vinci (1452–1519) not being widely known to his contemporaries. The major contributions of Vesalius were not in physiology but in anatomy and in the demonstration that Galen was capable of error (though he himself was not without error).

At the opening of the seventeenth century the important event for all science was the appearance (in 1600) of William Gilberd's[5] classic book *De Magnete* (10, 11). The significance of this work was not only as a landmark for the future of the physical sciences and of electrophysiology through its dawning recognition of a difference between electricity and magnetism; it was the first book to advocate empirical methods and in this way heralded the scientific ferment of the eighteenth century. If one overlooks the last two chapters of *De Magnete*, the book is revolutionary in its experimental approach. It stood out alone in an age when scholasticism was concerned with classification on qualitative lines without measurement and without validation. Authoritative statements of the ancients were the guides, and induction from experiment was virtually unknown. Gilberd's book makes a plea for "trustworthy experiments and demonstrated arguments" to replace "the probable guesses and opinions of the ordinary professors of philosophy."

Gilberd was physician to Queen Elizabeth (whom he only just survived) and a sketch identified as a portrait of him appears in the contemporary drawing (now in the British Museum) made by William Camden, the Court Herald, of her funeral procession in 1603. A contemporary oil portrait of him painted in 1591 has been lost and remains to us only in engravings. Gilberd was born and lived part of his life in his father's house in Colchester in East Anglia; a portion of this house still stands and, at the time of writing, is being restored. This flowering of the scientific method came during the golden age of Elizabethan England; among Gilberd's contemporaries were Shakespeare, Walter Raleigh, Philip Sydney, John Donne, Christopher Marlow and Francis Bacon.

Francis Bacon has a place in the history of all sciences, for he took scientific method a step farther, to observation he added induction and to inference he added verification. Scientists before him were content with performing an experiment in order to make an observation; from this observation a series of propositions would follow, each being derived from its predecessor, not by experiment but by logic. (Bacon somewhat unjustly criticizes Gilberd for proceeding in this way.) Bacon's contribution to scientific method was to urge, in addition, the rigorous application of a special kind of inductive reasoning proceeding from the accumulation of a number of particular facts to the demonstration of their interrelation and hence to a general conclusion. This was indeed a new instrument, a *Novum Organum* (12). By its application he overthrew reliance on authority of the ancients and opened the way for planned experiment. Although he had no place in his method for the working hypothesis, and his forms of induction and deduction are scarcely those of the modern methodology, they were of considerable influence in its development. The intelligent lines of Bacon's face can be seen in his portraits. John Aubrey (13) tells us that he "had a delicate, lively hazel eie" and that "Dr. Harvey told me it was like the eie of a viper."

The first major work in physiology exemplifying

10. GILBERD, WILLIAM (1540 (or 1544)–1603). *De Magnete, Magnetisque corporibus; et de magno magnete tellure; Physiologica nova plurimis et argumentis et experimentis demonstrata.* London: Peter Short, 1600; translated into English by the Gilbert Club, *William Gilbert of Colchester, physician of London.* London: Chiswick Press, 1900.
11. *Ibid.* (2nd ed.) (posthumous). Gotzianio in Stettin, 1633. This book, far rarer than the first edition, carries more plates than the original, and has some additions by Wolfgang Lochmann of Pomerania (1594–1643).
12. BACON, FRANCIS (1561–1626). *Novum Organum.* 1620; translated into English by Kitchin. Oxford, 1855.
13. AUBREY, JOHN (1626–1697). *Brief Lives set Down 1669–1696*, edited by Andrew Clark. Clarendon Press, 1898, vol. 2.

[5] The spelling of Gilberd's name follows the form seen on his portrait and memorial tablet; his name on his book is spelled Gilbert.

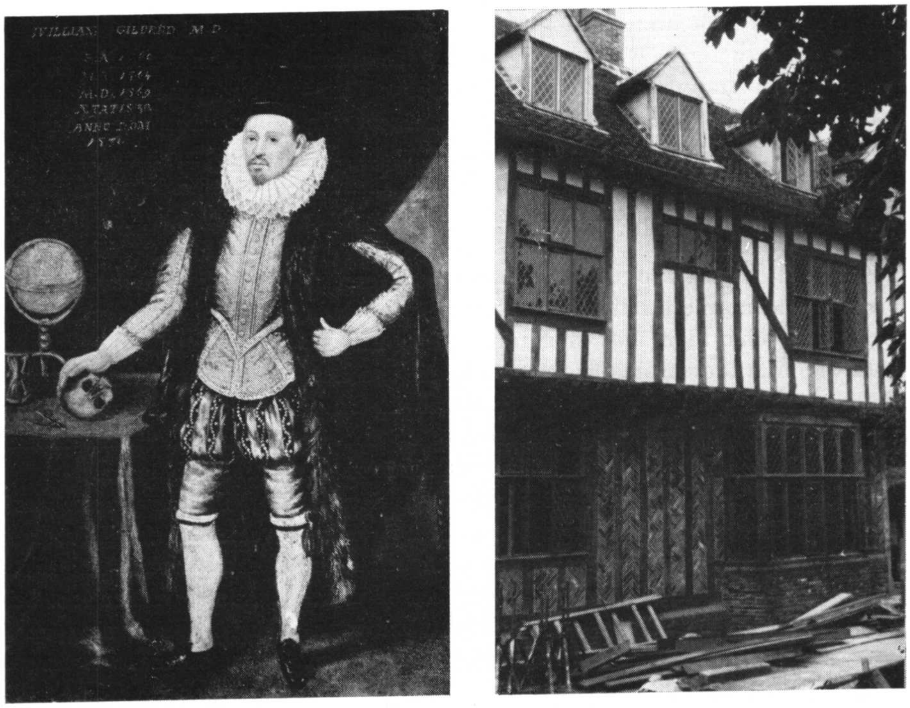

FIG. 1. Portrait of William Gilberd from an oil painting on wood, found by Silvanus P. Thompson in an antiquary's shop. The artist and the authenticity of the date on this portrait are unknown. The portrait is now in the possession of Miss Helen G. Thompson, by whose courtesy it is reproduced here. The photograph of 'Tymperleys,' Gilberd's home at Colchester, was taken in 1957 when the house was undergoing extensive restoration. A portion only of the house dates from Gilberd's time. (Photograph by courtesy of Dr. G. Burniston Brown.)

Bacon's methodology was not on the nervous system but on the circulation of the blood. Harvey's magnificent treatise *De Motu Cordis* (14) was a model for workers in all branches of physiology to follow. This small book (it has only 72 pages) was the first major treatment of a physiological subject in dynamic rather than static terms. By experiment Harvey disproved the Galenist doctrine that the motion of the blood in the arterial and venous systems was a tidal ebb and flow, independent except for some leakage through 'pores' in the interventricular septum. By further designed experiments Harvey proved his own hypothesis "that the blood in the animal body is impelled in a circle, and is in a state of ceaseless motion." Harvey had advanced this hypothesis in 1616 but, as a forerunner of modern scientific method, had proceeded to verify it before publishing his book. But even this triumph of the empirical method did not unseat in Harvey's thinking the belief in a soul located in the blood ('anima ipsa esse sanguis') (15). Harvey was Galenist enough to accept the *rete mirabile* as the destination of the blood within the cranium, although doubt as to its existence in man had already been raised by Berengario da Carpi (16, 17) a hundred years before. Harvey (18) had his own views of nervous function. "I believe," he said, "that in the nerves there is no progression of spirits, but irradiation; and that the actions from which sensation and

14. HARVEY, WILLIAM (1578–1657). *Exercitatio anatomica de motu cordis et sanguinis in animalibus.* Frankfurt: Fitzeri, 1628; translated into English by Willius and Keys, Cardiac Classics, 1941, p. 19.

15. HARVEY, W. *Praelectiones anatomiae universalis.* London: Churchill, 1886. (Reprint of Harvey's Lumleian lecture 1616.)

16. BERENGARIO DA CARPI, GIACOMO (1470–1550). *Commentaria cum amplissimus additionibus super anatomia Mundini.* Bologna: Benedictis, 1521.

17. BERENGARIO DA CARPI, G. *Isagogae breves, perlucidae.* In: *Anatomiam humani corporis, ad suorum scholasticorum preces in lucem editae.* Bologna, 1522; translated into English by H. Jackson, under the title *A description of the Body of Man, being a practical Anatomy.* London, 1664.

18. HARVEY, W. *Praelectiones Anatomiae Universalis*, autotype reproduction edition. Philadelphia: Cole, 1886.

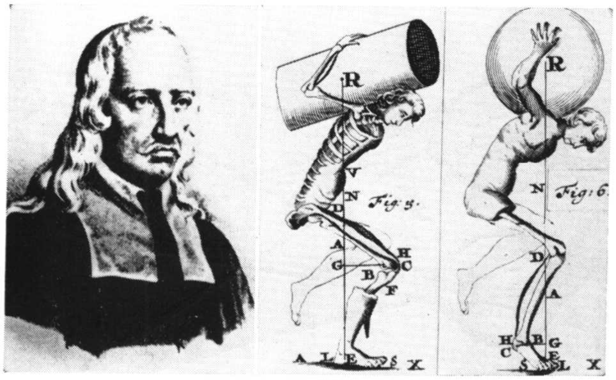

FIG. 2. Borelli and one of his sketches to show the center of gravity of man when carrying a load. (From Borelli, G.A. *De Motu Animalium*, 2nd ed., Leyden: Gaesbeeck, 1685.)

motion result are brought about as light is in air, perhaps as the flux and reflux of the sea."

That nerves might play a role in the working of the heart as a mechanical pump was first suggested by Borelli the Neapolitan, professor of mathematics at Pisa and later at Florence, who applied the reasoning of his discipline to physiology and evolved mechanical models for various bodily functions. His concept of the innervation of muscle was an initiation by the nervous fluid ('succus nerveus') of a fermentation in the muscle swelling it into contraction, for there were still many years to go before a dynamic concept of muscle was to emerge in spite of Harvey's demonstrations on the heart. Peripheral muscles were still regarded as passive structures rather like balloons to be inflated by nervous fluid or gaseous spirits reaching them through canals in the nerves. Borelli, by an ingenious experiment in which he submerged a struggling animal in water and then slit its muscles, demonstrated that the spirits could not be gaseous since no bubbles appeared in spite of the violent contractions. It was this experiment that led him to the suggestion of a liquid medium from the nerve, mixing in the muscle to cause a contraction by explosive fermentation ('ebullitio et displosio') (19).

Giovanni Alphonso Borelli was a member of the group of experimental scientists banded together in the Accademia del Cimento under the patronage of the science-loving Medici brothers in Florence. This small scientific society, successor to the Lincei, existed for only a decade but was typical of the independent groups centered on laboratory experiment that were to spring up in independence of the universities where the scholars had still not looked up from their books. Few as they were (there were only nine members) these laboratory scientists of the Accademia were to have a far-reaching though delayed influence on European thought, for in the final year of the academy's existence they published their proceedings (20). Founded entirely on empirical methodology, this was a truly scientific text. It was, however, written in Italian although soon translated into English, and it did not reach the scientific world at large until Petrus van Musschenbroek of Leyden made a Latin translation (21). It was this book that, for example, influenced Stephen Hales so greatly in his experimental work. The volume included only one series on animal experimentation, but almost all the rest deals with the physics which are basic to the work a physiologist does in his laboratory.

To his contemporary, Descartes, Borelli owed his application of mathematics to muscular action. This pungent philosopher, who rarely did an experiment, wrote a text that was to influence all experimenters, *The Discourse on Method* (22). It is not experimental method that he discusses, but his own method of thought, his theory of knowledge.[6] Scientists had just begun to look around them to observe nature and to let the statements about her by the ancients lie in the books when they had to meet a new and brilliant challenge; mathematics was the tool they were to use. Mathematics would not only elucidate the laboratory experiment but would provide the basis for an all-embracing theory of science.

This great man bred in the gentle landscape of Touraine was to devote his life to a search for the truth, seeking for himself a quiet environment for free thinking.[7] This he found for 25 years in the

19. BORELLI, GIOVANNI ALFONSO (1608–1679). *De motu animalium* (published posthumously). Rome: Bernado, 1680–1; a small section has been translated into English by Michael Foster. *Lectures on the History of Physiology*. Cambridge: Cambridge, 1901.

20. *Saggi di naturali esperienza fatte nell Accademia del Cimento*, edited by L. Magalotti. Florence, 1667; translated into English by Richard Waller. *Essayes of Natural Experiments made in the Accademie del Cimento*. London, 1684.

21. VAN MUSSCHENBROEK, PETRUS (1692–1761). *Testamina Experimentorium Naturalium captorum in Accademia del Cimento*. Leyden, 1731.

22. DESCARTES, R. *Discours de la Méthode*. 1637; English translation by E. S. Haldane and G. R. T. Ross. *Philosophical Works of Descartes*. Cambridge: Cambridge, 1904.

[6] "Méthode de bien conduire sa raison, pour trouver la verité dans les sciences."

[7] "Cum nil dignum apud homines scientia sua invenisset, eremum ut Democritus aliique veri Philosophi elegit sibi juxta Egmundum in Hollandia, sibique solitarius in villula per 25 annos remansit, admirandaque multa meditatione sua detexit" (Borel, p. 9).

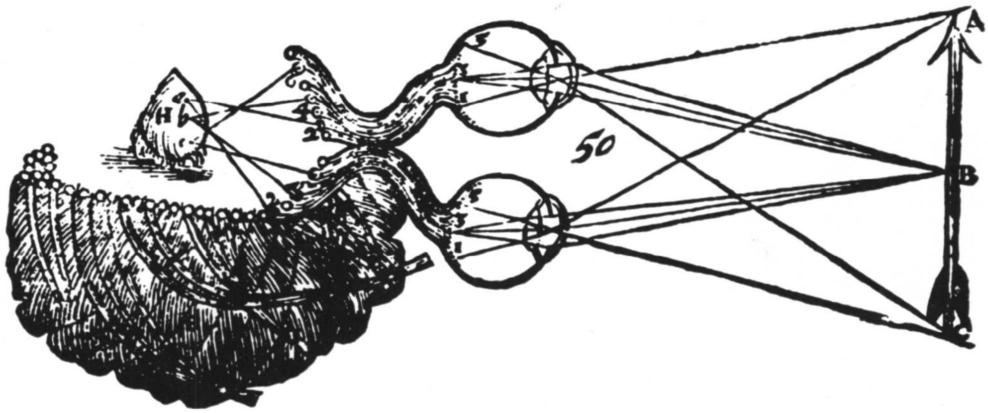

FIG. 3. René Descartes and his concept of the pineal gland. The photograph is from the portrait by Franz Hals in the Louvre, and the diagram is taken from de la Forge, Louis. *Traité de l'Esprit de l'Homme, de ses Facultéz, de ses Fonctions, et de son Union avec le Corps. Suivant les principes de Mr. Descartes*. Geneva: Bousquet, 1725.

village of Egmond in liberal Holland, though even here he could not entirely escape being hounded by bigots. The mistake he made that the world regrets was to leave a milieu so congenial to his philosophic nature for the cold of Sweden and the exacting demands of Queen Christina. There, within a year, he died. His striking face with the intelligent eyes and quizzical eyebrow has been preserved for us in the fine portrait by Franz Hals that hangs in the Louvre.

A great man has many 'lives' written about him but those set down by his contemporaries usually have a special flavor. In the case of Descartes, the short account of his life and his philosophy written by Borel (23) (the microscopist) in 1669 gives one the feeling of bridging the centuries. Borel gives a list of the manuscripts found in Stockholm at Descartes's death in 1650, including the early treatise he wrote on music when he was only 22. Several of his letters were found, some of which Borel reproduces. The letters date from 1632 and give an intimate glimpse of the struggle Descartes had to face in overcoming resistance to his theories among some of his contemporaries.

23. BOREL, PIERRE (1620–1689). *Vitae Renati Cartesii, Summi Philosophi Compendium*. Frankfurt: Sigismund, 1676.

[8] "It is an error to suppose the soul supplies the body with its heat and its movements." *Passions de l'Âme*, Article 5.

Descartes (24, 25), having become convinced that in mathematics lay the tool for a unified theory of all science, had now to explain its role in physiology. It followed logically that the animal body and all its workings was a machine, the operation of this machine being directed from a control tower. In the brain with its bilateral development, the singly represented pineal body was chosen by Descartes to play this master role and (in man) it was given the added responsibility of housing the soul. In the concept of the body as a machine, energized not by an immaterial anima[8] but by the external world impinging on it, lies a germ of the idea of reflex activity.

To coming generations of neurophysiologists Descartes bequeathed the notion that impressions from the external world were conveyed by material animal spirits to the ventricles and there directed by the pineal gland into those outgoing tubular nerves that could carry them to the part of the body the subsequent action of which would be the appropriate one. In animals this was presumed to be a purely mechanical action, but in man the soul, resident in the pineal, could have some say in the direction taken by this

24. DESCARTES, RENÉ (1596–1650). *Passions de l'Âme*. Amsterdam, 1649.
25. DESCARTES, R. *De homine figuris, et latinate donatus a Florentio Schuyl*, posthumous Latin version by Schuyl. Leyden: Moyardum & Leffen, 1662; first French edition, *Traité de l'Homme*, 1664; second French edition, 1677.

central relay. Descartes recognized, however, that perhaps some of these actions lay outside the control of the will, citing as examples involuntary blinking and the withdrawal of the hand on burning.

To neurophysiologists Descartes bequeathed another seed—what was later to be known as the reciprocal innervation of antagonist muscles. In order to ensure that while animal spirits were flowing into one set of muscles the opposing set should relax, he argued that the latter must have their supply of spirits blocked and he postulated that this must be effected by valves. Whether or not he was influenced in his thinking by Harvey's explanation of the valves of the veins is not known, although he was certainly aware of, and had commented on, Harvey's discoveries.[9] Descartes was a member of what a subsequent irreverent generation was to call 'the balloonists.' Apparently unaware of Borelli's experiments, he thought the animal spirits to be "like a wind or a very subtle flame" and that "when they flow into a muscle they cause it to become stiff and swollen, just as air in a balloon makes it hard and stretches the substance in which it is contained."

A young contemporary of Descartes, though less directly influenced by him than was Borelli, was William Croone who was working on muscle action. He too thought that the nervous 'juice' must interact in some way with the muscle (26). The "spiritous liquid" flowed in, mixed with "the nourishing juice of the muscle," and then the muscle "swell'd like a Bladder blown up." Later (27) Croone was to modify this to a number of small bladders for each muscle fiber. Just as Borelli had been a founding member of a scientific society, so was Croone. He was one of the original group who in England formed the Royal Society, a society which unlike the Cimento has continued to flourish and in which to this day eminent scientists not only discuss but demonstrate their experiments before the members. The Royal Society has several distinguished lectureships, among which is the Croonian Lecture founded by the widow of William Croone.

The Royal Society of London received its charter in 1662, being founded for the promotion of 'Natural Knowledge,' and it numbered among the founding members many whose contributions are fundamental to physiology. The moving spirit was Robert Boyle, the 'father of chemistry' (whose first published work was, however, on *Seraphick Love*). Famous for his law (28) of gaseous pressures, he made his most directly physiological experiments on the respiration of animals. It was still many years before physiologists were to elucidate the effects of anoxia on the nervous system, and another hundred years were to pass before Priestley's and Lavoisier's work on oxygen, but Boyle, by using an ingenious compression chamber, demonstrated that air is essential for life. Almost unnoticed at the time, but since then perhaps overpraised, were the observations of John Mayow (29) on the chemistry of respiration. His publication preceded (although his work was contemporary with) the somewhat similar experiments of the Accademia del Cimento.

In the early seventeenth century emphasis on the search for a chemical foundation for living phenomena characterized for the most part work in Holland and England in contrast to the physical and mathematical approach of the Italians and the French. The two contrasting schools of thought were long to be known by the clumsy names of the iatrochemical and iatromechanical schools. Iatrochemistry, on the rather shaky foundations given to it by van Helmont (1577–1644) and by Sylvius (de La Boë) (1614–1672), provided the approach to the study of the nervous system of Thomas Willis, Sedleian Professor of Natural Philosophy at Oxford (30). Willis, whose clinical achievements outshone his scientific acumen, is recognized in neurology for his description of the circle of Willis and his dissection of the spinal accessory nerve. (Galen had identified only seven pairs of cranial nerves.) Willis was a close colleague at Oxford of Richard Lower, the Cornishman, champion of the theory that spirits flowing into the heart from

26. Croone, William (1633–1684). *De ratione motus musculorum* (published anonymously). London: Hayes, 1664.

27. Croone, W. *An Hypothesis of the Structure of the Muscle, and the Reason of its Contraction.* Hooke's Philosophical Collections, No. 11. London, 1675.

28. Boyle, Robert (1627–1691). *New experiments physico-mechanical, touching the spring of the air, and its effects, made, for the most part, in a new pneumatical engine.* Oxford: W. Hall, 1660.

29. Mayow, John (1645–1679). *Tractus Duo, quorum prior agit De Respiratione: alter De Radutiones.* Oxford: Hall, 1668.

30. Willis, Thomas (1621–1675). *Cerebri anatome: cui accessit nervorum descriptio et usus. (De systemate nervoso in genere)*, illustrated by Sir Christopher Wren. London: Flesher, 1664; translated into English by S. Pordage. London: Dring, Harper and Leigh, 1683.

[9] Letter to Mersenne dated 1632, quoted in *Oeuvres Complètes de Descartes*, edition of Adam and Tannery, Paris: Cerf, 1897–1910, vol. II, p. 127.

its nerves were what caused it to beat (31). Lower's more spectacular achievement was the apparent transfusion of blood, first in dog and then in man (32, 33). We are surprised today that the man survived as long as he did, for the blood donor was a sheep.

Thomas Willis had added to the prevalent Galenic ideas of nervous function the concept that the soul had two parts which he likened to a flame in the vital fluid of the blood and a light in the nervous juice. When they met in the muscle, they formed a highly explosive mixture which inflated the muscle. Yet even before the seventeenth century had run out, a voice was raised against such visionary explanations. Stensen (34), the great Danish anatomist, writing from Florence in 1667, stated unequivocally that "Animal spirits, the more subtle part of the blood, the vapour of blood, and the juice of the nerves, these are names used by many, but they are mere words, meaning nothing."

The seventeenth century, or *grand siècle* as it was known to Europe, had been gloriously opened by the *De Magnete* and gone on to the achievements of Galileo, Kepler, Huygens, Leibniz and Newton, and, although these were essentially achievements in mathematics, physics and astronomy, all branches of science were fermenting with the implications of these discoveries. The break with dogma was now more than a crack, though the *Index Librorum Prohibitorum* fought a delaying action. The men of the arts were liberal in their championship of the scientists. John Milton's *Areopagitica* (35) is a clarion call for freedom of knowledge and distribution of books. Milton was a young contemporary of Galileo and went to see him in his old age. There is a poignancy about this visit to the old blind astronomer from the poet about to become blind.

The students of the nervous system had the hardest fight against dogma for in their province lay the structures most suspect as being the guardians of man's soul. But ranked behind them and influential on them were some of the greatest philosophers of their time. Prominent among these was Locke (36), the father of empiricism. Born in the West of England and trained as a physician, this man with his colorless personality and his clumsy prose was to channel the efforts of the next several generations of workers on the nervous system into a search for the physiology of the mind. For his *Essay on Humane Understanding* he received immediate recognition and monetary reward, obtaining for it more than was paid to John Milton for *Paradise Lost.*

Straddling like a colossus the division between the seventeenth and eighteenth centuries is Newton, friend and correspondent of Locke, though to scientists it is perhaps a bit disappointing to find that the subject of their correspondence was the interpretation of the New Testament (biblical history was a life-long interest of Newton). Newton's insight into the movement and forces of nature led him to make some tentative suggestions about the working of the nervous system, and these were noted by the physiologists of the time. There is scarcely a single neurophysiologist of the eighteenth century who does not explicitly attempt to align his findings with these conjectures of Newton.

In the General Scholium (37) which he added to the second edition of the *Principia* (26 years after its first publication), Newton included a speculation. This was the idea of an all-pervading elastic aether "exceedingly more rare and subtle than the air," which he again suggested in the form of a question in the series of Queries added to the second English edition of his *Opticks* (38). Applying this suggestion to the nervous system, he said, "I suppose that the Capillamenta of the Nerves are each of them solid and uniform, that the vibrating Motion of the Aetherial Medium may be propagated along them from one End to the other uniformly, and without interruption. . . ." It is easy to understand how eagerly such a statement would be received by those who accepted the idea of a nervous principle running down the nerves but were worried that they knew of no fluid sufficiently swift and invisible. Newton's rather sketchy suggestion was therefore eagerly embraced by many of his contemporaries, one of whom, Bryan Robinson,

31. Lower, Richard (1631–1691). *Tractatus de Corde item de Motu & Colore Sanguinis et Chyli cum Transitu.* London: Allestry, 1669; English translation by K. J. Franklin. *Early Science in Oxford.* Oxford, 1932, vol. 9.
32. Lower, R. The method observed in transfusing the blood out of one live animal into another. *Phil. Trans.* 1: 353, 1665–6.
33. Lower, R. and E. King. An account of the experiment of transfusion, practised upon a man in London. *Phil. Trans.* 2: 1557, 1667.
34. Stensen, Nicholas (1638–1686). *Elementorum myologiae specimen.* Florence: Stella, 1667, p. 83.
35. Milton, John (1608–1674). *Areopagitica. A speech for the Liberty of Unlicensed Printing to the Parliament of England.* 1644.
36. Locke, John (1632–1704). *An Essay concerning Humane Understanding.* London: Holt, 1690.
37. Newton, Isaac (1642–1727). *Principia.* London: 1687; edition with General Scholium, 1713.
38. Newton, I. *Opticks* (2nd ed., 24th Query). London: 1717.

Regius Professor of Physic at the University of Dublin, even went so far as to claim that "Sir Isaac Newton discovered the Causes of Muscular Motion and Secretion" (39).

At the opening of the eigthteenth century the science of the nervous system had reached different levels in the various countries of Europe. In Germany in the first half of the century the Thirty Years War had brought science almost to a standstill, and in the fields of chemistry and physiology this stagnation developed into a retrogression owing to the emergence of an extremely influential figure, Georg Ernst Stahl. In opposition to both the chemical and mathematical schools, Stahl set back the clock by the reintroduction of an immaterial anima which he held to be the sole activating principle of the body parts (40). The latter were regarded as having no dynamic properties of their own, being essentially passive structures. Since the search for an immaterial agent lies outside the scope of science, Stahl's doctrines, promulgated with arrogance and dogmatism, virtually extinguished experimental inquiry among his followers. Yet even writers sympathetic to his viewpoint granted that in attempting to follow his arguments one became "involved in a labyrinth of metaphysical subtlety" (41). The metaphysical approach of Stahl later came under criticism from Vicq d'Azyr (42) who suggested that the invention of an imaginary soul to resolve those phenomena that could not yet be explained by the laws of physics and chemistry was merely a cloak for ignorance. van Helmont did not escape the same criticism.

In opposition to humoral or vitalistic concepts of nervous and muscular activity was a prominent champion of a 'solidist' theory, Giorgio Baglivi. This young man, whom Pope Innocent XII had appointed to be professor of the theory of medicine and anatomy at Rome, put emphasis on the fibers of the muscles and the nerves, and so foreshadowed the importance that was to be given in the eighteenth century to the intrinsic structural properties of these tissues. He developed a theory (43) of an oscillatory movement of nerve fibers in order to account for both efferent and afferent activity and envisaged the dura mater as the source of these movements and the recipient of the returning oscillation.

FIG. 4. Giorgio Baglivi rising like a phoenix from the flames.

The leading medical center in Europe at this time was the University of Leiden. The empirical approach was urged by the physicist S'Gravesande (44) who advised that "It is Nature herself that should be examined as closely as possible . . . progress may be slow, but what we find will be certain." Petrus van Musschenbroek (45), who had come to the Chair of Physics at Leiden from Utrecht in 1740, had in a discourse on scientific method emphasized that physics should stand apart from metaphysics, that experimental analysis should antecede synthesis, that in the collection of evidence the exception should not be ignored, and that argument by analogy was fraught with danger. Yet it was essentially by analogy that the early eighteenth century viewed the func-

39. ROBINSON, BRYAN (1680–1754). *A treatise of the Animal Oeconomy* (3rd ed.). London: Innys, 1738.
40. STAHL, GEORG ERNST (1660–1734). *Theoria Medica Vera Physiologiam et Pathologium, tanquam Doctrinae Medicae Partes veres Contemplativas e Naturae et Artis veris fundamentis.* Halle, 1708.
41. BOSTOCK, JOHN (1773–1846). *Sketch of the History of Medicine from its origin to the commencement of the nineteenth century.* London: Sherwood, Gilbert & Piper, 1835.
42. VICQ D'AZYR, F. (1748–1794). *Oeuvres de Vicq d'Azyr.* Paris, 1805, vol. 4.
43. BAGLIVI, GIORGIO (1668–1707). De fibra motrice et morbosa. In: *Opera Omnia.* Leyden: Antonii Servant, 1733.
44. S'GRAVESANDE, WILHELM JACOB (1688–1742). *Physices Elementa Mathematica Experimentis confirmata sive Introductio ad Philosopham Newtonianam.* 2nd ed., 1725; 3rd ed., 1742, 2 vols. Leiden.
45. VAN MUSSCHENBROEK, PETRUS (1692–1761). *Discours à l'Organisation de l'Expérience.* 1730. (His swansong as Rector at the University of Utrecht.)