PROGRESS IN BRAIN RESEARCH

VOLUME 41

INTEGRATIVE HYPOTHALAMIC ACTIVITY

EDITED BY

D.F. SWAAB

AND

J.P. SCHADÉ

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List of Contributors

E. ANDERSON, NASA Ames Research Center, Moffett Field, Calif. 94035, U.S.A.

J. ARIËNS KAPPERS, Netherlands Central Institute for Brain Research, IJdijk 28, Amsterdam, The Netherlands.

C. A. BAILE, Smith, Kline and French Laboratories, West Chester, Philadelphia, Pa., U.S.A.

G. J. BOER, Netherlands Central Institute for Brain Research, IJdijk 28, Amsterdam, The Netherlands.

K. BOER, Netherlands Central Institute for Brain Research, IJdijk 28, Amsterdam, The Netherlands.

B. BOHUS, Rudolf Magnus Institute for Pharmacology, Medical Faculty, University of Utrecht, Vondellaan 6, Utrecht, The Netherlands.

P. F. BRAIN, Department of Zoology, University College of Swansea, Swansea, SA2 8PP, Wales, Great Britain.

J. A. M. DE ROOIJ, Department of Experimental Neurology, Radboud University, Nijmegen, The Netherlands.

L. DE RUITER, Department of Zoology, The University, Groningen, The Netherlands.

R. A. C. DE VRIES, Netherlands Central Institute for Brain Research, IJdijk 28, Amsterdam, The Netherlands.

D. DE WIED, Rudolf Magnus Institute for Pharmacology, Medical Faculty, University of Utrecht, Vondellaan 6, Utrecht, The Netherlands.

B. T. DONOVAN, Department of Physiology, Institute of Psychiatry, De Crespigny Park, London, SE5 8AF, Great Britain.

G. DÖRNER, Institute of Experimental Endocrinology, Humboldt-University, Berlin, G.F.R.

J-P. DUPOUY, Laboratory of Comparative Physiology, 9 quai Saint-Bernard, Paris 5e, France.

R. G. DYER, Department of Anatomy, University of Bristol, Bristol, BS8 1TD, Great Britain.

C. M. EVANS, Department of Zoology, University College of Swansea, Swansea, SA2 8PP, Wales, Great Britain.

J. M. FORBES, Department of Animal Physiology and Nutrition, Kirkstall Laboratories, Vicarage Terrace, Leeds, LS5 3HL, Great Britain.

R. GUILLEMIN, The Salk Institute, La Jolla, Calif. U.S.A.

W. HAYMAKER, NASA Ames Research Center, Moffett Field, Calif. 94035, U.S.A.

J. HERBERT, Department of Anatomy, University of Cambridge, Cambridge, CB2 3DY, Great Britain.

O. R. HOMMES, Department of Experimental Neurology, Radboud University, Nijmegen, The Netherlands.

W. J. HONNEBIER, Department of Obstetrics and Gynecology, Wilhelmina Gasthuis, Amsterdam, The Netherlands.

H. G. JANSEN, Department of Anatomy, Erasmus University, Rotterdam, The Netherlands.

A. JOST, Laboratory of Comparative Physiology, 9 quai Saint-Bernard, Paris 5e, France.

U. JÜRGENS, Max-Planck-Institute for Psychiatry, Kraepelinstr. 2, Munich 40, G.F.R.

A. J. KREIKE, Department of Anatomy, Erasmus University, Rotterdam, The Netherlands.

H. J. LAMMERS, Department of Anatomy, Radboud University, Nijmegen, The Netherlands.

S. LEVINE, Department of Psychiatry, Stanford University School of Medicine, Stanford, Calif. 94305, U.S.A.

D. W. LINCOLN, Department of Anatomy, The Medical School, University Walk, Bristol, BS8 1TD, Great Britain.

A. H. M. LOHMAN, Department of Anatomy, Radboud University, Nijmegen, The Netherlands.

B. G. MONROE, Department of Anatomy, University of Southern California, Los Angeles, Calif. 90033, U.S.A.

W. K. PAULL, Department of Anatomy, University of Southern California, Los Angeles, Calif. 90033, U.S.A.

M. J. PEDDIE, Department of Physiology, Institute of Psychiatry, De Crespigny Park, London, SE5 8AF, Great Britain.

C. PILGRIM, Faculty of Morphology and Anatomy, Fachbereich Biologie, Universität Regensburg, Postfach 84, Regensburg, G.F.R.

A. E. POOLE, Department of Zoology, University College of Swansea, Swansea, SA2 8PP, Wales, Great Britain.

M. RIEUTORT, Laboratory of Comparative Physiology, 9 quai Saint-Bernard, Paris 5e, France.

D. F. SALAMAN, Department of Anatomy, The Medical School, University of Bristol, Bristol, BS8 1TD, Great Britain.

J. L. SLANGEN, Rudolf Magnus Institute for Pharmacology, University of Utrecht, Medical Faculty, Vondellaan 6, Utrecht, The Netherlands.

A. R. SMITH, Netherlands Central Institute for Brain Research, IJdijk 28, Amsterdam, The Netherlands.

J. M. STERN, Department of Psychiatry, Stanford University School of Medicine, Stanford, Calif. 94305, U.S.A.

R. STOECKART, Department of Anatomy, Erasmus University, Rotterdam, The Netherlands.

D. F. SWAAB, Netherlands Central Institute for Brain Research, IJdijk 28, Amsterdam, The Netherlands.

H. VAN DIS, Netherlands Central Institute for Brain Research, IJdijk 28, Amsterdam, The Netherlands.

N. E. VAN DE POLL, Netherlands Central Institute for Brain Research, IJdijk 28, Amsterdam, The Netherlands.

P. VAN DER SCHOOT, Faculty of Medicine, Erasmus University, Rotterdam, The Netherlands.

TJ. B. VAN WIMERSMA GREIDANUS, Rudolf Magnus Institute for Pharmacology, Medical Faculty, University of Utrecht, Vondellaan 6, Utrecht, The Netherlands.

J. G. VEENING, Department of Zoology, The University, Groningen, The Netherlands.

M. J. WAYNER, Brain Research Laboratory, Syracuse University, 601 University Avenue, Syracuse, N.Y. 13210, U.S.A.

P. R. WIEPKEMA, Department of Zoology, The University, Groningen, The Netherlands.

Preface

This volume contains the proceedings of the VIIIth International Summer School of Brain Research which has been organized by the Netherlands Central Institute for Brain Research, Amsterdam. For this conference the topic "Integrative Hypothalamic Activity" was chosen in order to stress the special properties which the hypothalamus has as one of the most important integration centres of the brain, rather than organizing lectures on different and separate subjects related to this part of the diencephalon. The interest of a number of research workers at the Institute and recent work performed by them on the hypothalamus have also been of importance in shaping the programme. This is the reason why special emphasis has been laid on the role played by the hypothalamus in sexual differentiation, in the control of parturition and in several aspects of behaviour while also the influence exerted by the pineal gland on the hypothalamo–hypophyseo–gonadal axis and on the magnocellular hypothalamic neurosecretory system is dealt with. As it was realized that structural principles lie at the base of physiological phenomena, the programme, after an introductory paper on the history of hypothalamic research, started with lectures on hypothalamic morphology.

As our knowledge of hypothalamic morphology, histo- and biochemistry and the physiological implications of the many extrinsic and intrinsic neural and hormonal hypothalamic pathways is vastly growing, it seemed right to summarize and integrate at least part of the many results obtained for an auditorium of young research workers for whom these Summer Schools are intended.

My thanks are due to all participants contributing so many valuable papers and taking such a lively part in the discussions which have been very fruitful. I am also most grateful for the invaluable help of Drs. Swaab and Schadé, the editors of this volume, in constituting the programme and in organizing this Summer School and to Miss J. Sels for her editorial assistance.

J. ARIËNS KAPPERS
Central Institute for Brain Research
Amsterdam, The Netherlands

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Breakthroughs in Hypothalamic and Pituitary Research

EVELYN ANDERSON AND WEBB HAYMAKER

NASA Ames Research Center, Moffett Field, Calif. 94035 (U.S.A.)

INTRODUCTION

Sir Henry Dale (1957), in speaking of his student days, tells of learning physiology from Michael Foster's *Textbook of Physiology*, the 1891 edition. He says that the textbook was "curtly explicit in its account of the knowledge then available concerning the function of the pituitary body", for Foster wrote that "with regard to the purposes of the organ as a whole we know absolutely nothing". Dale goes on to say that this "is a statement which you may well imagine was not without an aspect of reassurance for a student with an examination in prospect". Today's students do not have that reassurance. In the past half century our knowledge, not only of the pituitary but also the hypothalamus, has undergone phenomenal growth and to attempt to grasp its significance is enough to boggle the mind of the specialist as well as the student; nor is it easy to single out the anatomists, physiologists and clinicians who over the years have been responsible for this tremendous growth and to say that these were the founders or the leaders. We must wait for Time to grade them as to the greatness of their contributions.

In accepting this assignment we were made bold by a story about Magendie which Olmsted (1938) relates in his biography of Claude Bernard regarding certain attitudes of Magendie which "forebade him to attempt to reconcile contradictory results. If he obtained one result in 1892 and another in 1893 it was all the same to him. He trusted future experiments to provide the missing explanation. Far from being ashamed of his complete lack of method in the conduct of his research, he was proud of it. He told Bernard: Everyone compares himself to something more or less majestic in his own sphere, to Archimedes, Michaelangelo, Galileo, Descartes, and so on. Louis XIV compared himself to the Sun: I am much more humble. I compare myself to a scavenger; with my hook in my hand and my pack on my back I go about the domain of science picking up what I can find" (p. 25).

We have gone through the pages of the history of the hypothalamus and the pituitary, picking up some of the great findings, which you, at this meeting, will undertake the task of integrating into a complete story. Of the many contributors, some have led the way in major breakthroughs in hypothalamic and pituitary research which have permitted others to carry through to the development of this knowledge. It is to these

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Fig. 1. François Magendie (1783–1855). By courtesy of the Bibliothèque de l'Académie Nationale de Médecine cliché Assistance Publique (No. 85-1666, Médecins).

contributors whose breakthroughs we so often take for granted that we wish to pay our respects in this discussion.

THE RETE MIRABILE AND THE PITUITARY

The pituitary and its infundibulum appeared on the horizon, centuries before the hypothalamus came to be known. Galen (129(?)–199 A.D.) of Pergamon was the first to recognize their existence and to comment on their function. According to Sarton (1954), "Galen's mind was quick and tidy, but clouded by an excessive fondness for theory and classification.... He was honest and sincere but egotistic, vain, complacent, irritable, and jealous" (p. 79).

Many of Galen's studies were based on dissection of the brains of oxen, goats, swine and monkeys (*Macaca inua* and *Macaca mulatta*), in which he described not only the pituitary and the infundibulum but also the 4 chambers (ventricles) of the brain, the fornix, the corpus callosum, the pineal, and the corpora quadrigemina. Among the chambers of the brain were the two lateral ones, which he called the "thalamus" (literally, "bridal chamber"). To Galen the chambers at the base of the brain supplied "animal spirit" to the optic nerves — hence, *thalami nervorum opticorum*,

Fig. 2. Claudius Galen (129(?)–199 A. D.). Portrait by courtesy of the Biomedical Library, Univ. of California at Los Angeles.

and its English equivalent, "optic thalamus", a term that still lingers with us (Fulton, 1943, p. 252). Galen must have seen the hypothalamus many times but found nothing remarkable to say about it.

Galen described an exceedingly prominent network of blood vessels surrounding the pituitary, which came to be called the *rete mirabile* when translated from Greek into Latin. According to Clarke and O'Malley (1968), Galen considered that "the vital spirit in the blood from the heart was changed into animal spirit in the *rete mirabile* and then, as mediator of all the brain's activities, stored in the ventricles" (p. 758). The *rete mirabile* seems to have been of central importance to Galen. He states that "the plexus that embraces the (pituitary) gland itself and extends for a great distance posteriorly is the most remarkable of bodies found in this region" (p. 758). Kuhlenbeck (1973) reminds us that such *retia mirabilia* are found in various mammals, including Edentata, Ungulata, Carnivora, Sirenia, and Cetacea, and that they are analogous to the (arterial) renal glomeruli and the (venous) portal sinusoids. O'Malley (1964) remarks that Galen's acceptance of the *rete mirabile* as a structure in the human

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brain was clearly in error (p. 9). To us, on the other hand, Galen's *rete mirabile* coincides with the diminutive aggregate of vessels which Duvernoy (1972) referred to as a "surface capillary network", as a glance at the India-ink perfusion preparations published by him and by other anatomists will testify. Although in man this "rete" has been greatly reduced in magnitude, in our opinion it nonetheless qualifies in its own right as a *rete mirabile*. In short, in a sense we are in agreement with Galen on this point.

Galen's influence dominated medicine for well over a thousand years, until interrupted by Vesalius (1514–1564) with the publication of his great treatise on anatomy, *De Humani Corporis Fabrica*, in Basle in 1543. At the time, Vesalius was only 27 years of age. Singer (1946, 1957) deduces that "Vesalius was a strong, resolute man of clear, firm-knit, and unsubtle mind ...", and that he was a "noisy, bustling, exhibitionist genius".

Vesalius is said to have had the services of the artist, Jan Stefan van Kalkar, who had been a pupil of Titian. However, as is brought out by Saunders and O'Malley (1950), "There is no more contentious and difficult subject respecting the Vesalian

Fig. 3. Andreas Vesalius (1514–1564). Portrait by courtesy of the National Library of Medicine, Bethesda, Md.

problem than the question of the identity of the artist or artists responsible for the Vesalian illustrations" (p. 25). Vesalius' accurate descriptions and the artists' (including Titian's?) documentation of the dissections by over 300 engravings and woodcuts made the *Fabrica* a breakthrough of greatest importance. "With Vesalius", according to Garrison, "the anatomy of the brain became modern with one bound" (see McHenry, 1969, p. 40).

Vesalius was born in Brussels, the son of the imperial court apothecary. Attracted at an early age to the study of anatomy, he meticulously dissected all the animals he could get hold of. He went to Paris to take up the study of medicine, particularly with a view to mastering human anatomy. But he learned little during his student days. One of his professors of anatomy, Winter von Andernach, was a learned student of classical literature who was the first to translate Galen's chief anatomical treatise from Greek into Latin. Although he taught anatomy, this professor had never done a dissection. So Vesalius had to learn for himself. He again dissected animals, and from time to time obtained human bones from cemeteries or he went to places of execution in search of material. He would study bones until he could identify them with closed eyes. His zeal brought him to the attention of his professors, who asked him to undertake the job of dissection. For the first time, Sigerist (1958) relates, he stood with scalpel in hand before a human corpse in front of an audience (p. 106). The outbreak of war made him leave Paris (in 1536).

It was at Padua (starting in 1537) that Vesalius' preparation of the *Fabrica* was undertaken. He was then only 22, and had been made professor at the University. Consistent with the detestable literary manners current at that time, Vesalius mercilessly attacked Galen. In a "childishly irritable and flatulently abusive" way, he pointed to Galen's many errors, and drummed away at the fact that Galen had never dissected a human body. At first he accepted Galen's *rete mirabile* as an anatomical fact, but later denied its existence (Clarke and O'Malley, 1968, p. 768), a point on which, in our opinion, Vesalius was correct so far as gross appearances went but otherwise was clearly in error. Vesalius disagreed with Galen's view that excretory ducts ran from the lateral ventricles to the cribra ethmoidalis, but accepted the view that the brain excreted waste material *(pituita)* through the infundibulum into the pituitary, whence it somehow passed into the nasopharynx (Rolleston, 1936, p. 42). Vesalius described this pituita (as interpreted by O'Malley, 1964, p. 9) as residue left from the ultrarefinement of animal spirit (the substance responsible for sensation and motion) that had reached the brain in the form of vital spirit from the heart.

One hundred years after Vesalius — in 1664 — Thomas Willis (1621–1675) published his memorable treatise, *Cerebri Anatome*, which far surpassed anything that had been published up to that time. In addition to anatomy, this treatise dealt with functions of the nervous system. This and the six other books he wrote marked the transition between medieval and modern notions of brain structure and function.

A man of no carriage and little discourse though very congenial, Willis had the most fashionable and lucrative medical practice in London. According to Sir Michael Foster (1901), "love of truth was in him less potent than love of fame" (p. 270). Certain other critics said he was neither erudite nor original and that much of his

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Fig. 4. Thomas Willis (1621–1675). Portrait by courtesy of the Biomedical Library, Univ. of California at Los Angeles.

success was attributable to the fertile mind of Richard Lower (1631–1691), who was assistant to Willis for at least 10 years. From his observations on the formation and circulation of the cerebrospinal fluid, and from a study of the mechanism of hydrocephalus, Richard Lower, in 1672, finally convinced Willis that nasal secretions do not filter down from the pituitary. In this view, Lower was in agreement with Conrad Schneider (1614–1680) of Wittenberg who had shown in 1655 that these secretions were the product of small glands in the nasal mucosa (see Mettler, 1947, p. 65).

Mention of Willis naturally leads to the arterial circle at the base of the brain. Others before Willis were aware of that circle. Among them was Gabriel Fallopius, a pupil of Vesalius, who mentioned it in 1561. Moreover, in 1632, which was 30 years prior to the publication of Willis' *Cerebri Anatome*, Guilio Casserio (1545–1605), a professor at Padua and one of Harvey's teachers, published an illustration of the base of the brain and its embracing arterial circle. Christopher Wren (1632–1723) was responsible for naming the circle after Willis. Wren, at the time a student at Oxford, was employed by Willis to prepare the anatomical plates of *Cerebri Anatome*, and in his sketch, inserted the caption, "circle of Willis". Willis had no reason to protest, for he had experimented extensively on the circle by squirting "a liquor dyed with ink" into peripheral cerebral vessels. Noting the appearance of dark spots on the cut surface of the brain, he concluded that the ink reached fine vessels in the brain substance. Willis went on to say that large vessels ("the fourfold chariot") running to the arterial

Fig. 5. Richard Lower (1631–1691). Portrait from the Wellcome Institute of the History of Medicine, London, England, by courtesy of the Trustees.

circle at the base of the brain, could, by way of their "mutual conjoinings", ... supply or fill the channels of all the rest of the cerebral vasculature, and thus prevent apoplexy. More than that, he found that some vestige of the ink reached vessels covering the base of the brain (Clarke and O'Malley, 1968, p. 778), bringing to better view the "surface capillary network", which as noted earlier, could well be a small rendition of Galen's *rete mirabile.*

INTIMATIONS OF HYPOTHALAMIC FUNCTION

Some 200 years after Willis and Lower — up to about 1875 — the hypothalamus as such was still unknown and the pituitary was considered inconsequential. Lo Monaco and van Rynberk (sic!), in two papers published in 1901, reminded their readers that the pituitary had long been regarded as an unpaired sympathetic ganglion, and that Sylvius and Magendie thought it a lymphatic gland having the function of collecting

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Fig. 6. Gérard A. van Rijnberk (1875–1953). Portrait by courtesy of Professor Paul E. Voorhoeve, Amsterdam.

cerebrospinal fluid and discharging it into the circle of Willis. In their rebuttal to these views, based on extensive experimental work, Lo Monaco and van Rynberk concluded that the pituitary was an involuted organ that had "no important function, neither general nor special". This publication originated from the laboratory of no less an authority than Luigi Luciani, Professor of Physiology and Rector of the University of Rome, where van Rynberk had gone to prepare his doctor's thesis. (For a brief biography of the distinguished van Rynberk, see Duyff, 1947.)

Following suit in 1908, Schäfer and Herring referred to the anterior lobe of the pituitary as not having any physiological effect. In 1909 the pituitary was defined in Murray's *New English Dictionary on Historical Principles, Vol. 7*, as "a small bilobed body of unknown function attached to the infundibulum at the base of the brain" (see Cushing, 1932, p. 10). Reflecting the same viewpoint, Thaon in his book on the pituitary published in 1907 mentioned that the posterior lobe presents only minimal interest. But well before the early 1900s and up into the 1920s, important events were occurring in the pathological and clinical fields in the form of case reports, each giving some inkling that the pituitary was a functioning organ. It was later in this period that the significance of the hypothalamus gradually came to be realized, though confusion persisted as to where to draw the line between the function exercised by the hypothalamus, on the one hand, and the function possessed by the pituitary, on the other.

Gastric ulceration from central lesions

The earliest intimation that the base of the brain was concerned in vegetative function came from Carl von Rokitansky's observation in 1842 that infectious lesions located in this region commonly were associated with grave gastric disturbances, often in the form of perforations and, occasionally, gastric hemorrhage. Rokitansky suggested that areas of softening of the stomach occurring in association with acute affections of the brain or its membranes were probably brought about by a reflex action of the esophageal and gastric branches of the vagus.

Rokitansky's views were put to the test by Moritz Schiff 3 years later — in 1845. He found in dogs and rabbits that unilateral cerebral lesions involving the thalamus and adjacent cerebral peduncle often led, after a few days, to softening of the stomach and occasionally to perforation. Soon afterwards — in 1854 — he found that much the same effect could occur following unilateral division of the pons or even hemisection

Fig. 7. Carl Freiherr von Rokitansky (1804–1878). Portrait by courtesy of the National Library of Medicine, Bethesda, Md. (Neg. No. 61-401).

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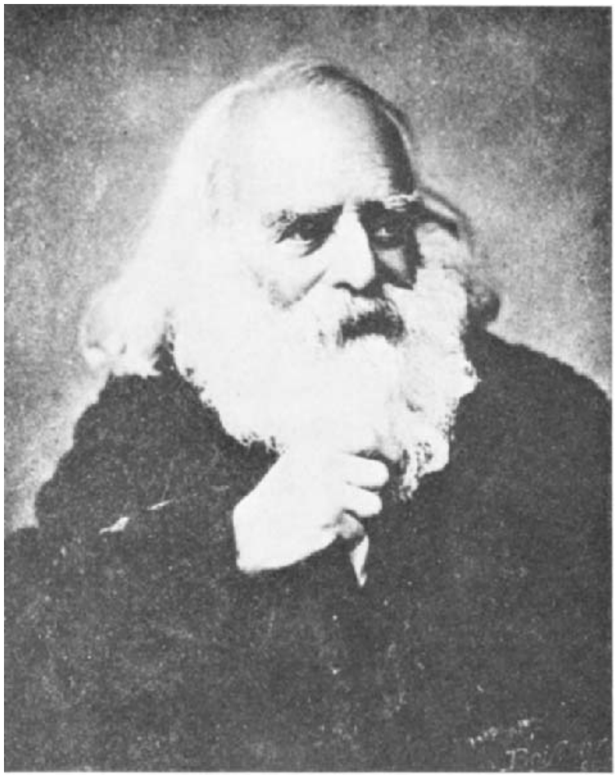

Fig. 8. Moritz Schiff (1823–1896). Portrait by courtesy of the National Library of Medicine, Bethesda, Md. (Neg. No. 68-486).

of the upper two segments of the spinal cord. Stimulation of certain structures (corpora quadrigemina, pons, and cerebral peduncle) caused gastric movements comparable to those elicited by vagus stimulation, and he found that these movements were blocked by division of the vagi. He also observed that stimulation of the splanchnics caused contraction of the vessels of the stomach. In a later summation (1867), Schiff anticipated the present-day distinction between the counterbalancing sympathetic and parasympathetic system and their role in the causation of lesions in the stomach and neighboring gut.

In the passing years more clinical cases of esophageal or gastric or duodenal softening or hemorrhage or perforation associated with central lesions got into the record: a gummatous interpeduncular tumor with softening of the right side of the pons and medulla oblongata associated with esophageal perforation (Hoffmann, 1868), a walnut-sized "sarcoma" of the meninges in the interpeduncular space associated with hyperemic softening of the stomach with numerous ecchymoses of the fundus (Arndt, 1874), and a median cerebellar tumor compressing the corpora quadrigemina and medulla oblongata associated with ecchymoses, extravasations, and hemorrhagic erosions of the stomach together with a markedly hyperemic and ecchymotic lower esophagus and duodenum (Arndt, 1888).

Fig. 9. Harvey Williams Cushing (1869–1939). Portrait by courtesy of Yale Univ. Art Gallery, gift of Mrs. Cushing; by John S. Sargent.

Nothing more of any substance on this subject appeared in the literature until Harvey Cushing's Balfour Lecture on *Peptic Ulcer and the Interbrain* delivered in 1931 and published the following year. Here he described all the kinds of cases that had been seen by Rokitansky. He stated that: "... direct stimulation of the tuber or of its descending fiber tracts, or what theoretically amounts to the same thing, a functional release of the vagus from paralysis of the antagonistic sympathetic fibers, leads to hypersecretion, hyperchlorhydria, hypermotility and hypertonicity especially marked in the pyloric segment. By the spasmodic contractions of the musculature, possibly supplemented by accompanying local spasms of the terminal blood-vessels small areas of ischemia or hemorrhagic infarction are produced, leaving the overlying mucosa exposed to the digestive effects of its own hyperacid juices" (p. 221–222). Cushing had a way of stating his ideas with ultimate clarity and logic, and with these few sentences he wiped out vagaries of the past and set the stage for the future.

Primary polydipsia of Nothnagel

Nothnagel, as early as 1881, reported on a condition which he called "primary

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Fig. 10. Hermann Nothnagel (1841–1905). Portrait by courtesy of the National Library of Medicine, Bethesda, Md. (Neg. 73-207).

polydipsia". He described the case of a man who was kicked by a horse, causing him to fall backward, striking the back of his head. Within half an hour he developed a fierce thirst, drinking up to 3 liters of water and beer within a period of 3 h, and only then did he begin to urinate. The man recovered quickly without other disabilities but the thirst persisted for about 4 days. Nothnagel postulated that the site of injury responsible for the polydipsia was in the floor of the fourth ventricle. This was the first suggestion that some part of the central nervous system was sensitive to water need. Subsequent studies on the hypothalamus by Bellows and Van Wagenen (1935), Hess and Brügger (1943), Andersson (1952, 1957), Andersson and McCann (1956), Stevenson (1949), and others, have consolidated this concept.

Hypersomnia

In the field of sleep–wakefulness, chief attention turned to the reticular activating substance (or system) when its functional significance became recognized through experimentation carried out by H. W. Magoun and Giuseppe Moruzzi toward the end of the Ranson heyday at Northwestern University (in Chicago) — around 1942–1943 — and soon afterwards at the University of California at Los Angeles in association with John D. French. An account of much of this work is given in Magoun's *The Waking Brain*, published in 1958 (see also French and Magoun, 1950). Moruzzi and Magoun (1949) demonstrated the importance of the brain stem reticular substance in conscious behavior and they also found that its electrocortical accompaniment was relatively independent of specific sensory and motor pathways. In monkeys, Moruzzi and Magoun and their associates found that the reticular activating substance occupied a fairly large area of the brain stem (from the mid-pons upward through the midbrain) well into the nonspecific nuclei of the thalamus, and extending into the posterior hypothalamus.

The observations of Magoun and Moruzzi were certainly a breakthrough, but the basic idea underlying this development had been presented some 12 years earlier — in 1937 — by Wilder Penfield. Penfield's hypothesis was that "the indispensible substratum of consciousness lies outside the cerebral cortex, ... probably in the diencephalon". In a further consideration of his concept, Penfield (1952) proposed that a neuron system centrally placed in the brain stem and connected equally with the two hemispheres could be described as biencephalic, but that "centrencephalic" was perhaps more descriptive; in the "brain stem" he included the thalamus. "Let us define the centrencephalic system", Penfield (1952) stated, "as that neurone system in the higher brain stem which has ... equal functional relations with the two cerebral hemispheres". Thus, Penfield's centrencephalic system coincided in considerable degree with what Magoun later called the reticular activating substance. Subsequently, to avoid misconceptions, Penfield and Jasper (1954) referred to the structures in question as the "centrencephalic integrating system", a subject on which Jasper again expounded in his Hughlings Jackson Lecture in 1959 (Jasper, 1960).

One could of course challenge the use of the work "integrating" in the context used by Penfield. Hartwig Kuhlenbeck (1954, 1957) suggests that the grisea of the "centrencephalic system" do not integrate (in the generally accepted sense of this term) but merely provide one of the several important "activating factors" required for the occurrence of such cortico-thalamic events as are correlated with consciousness; instead, Kuhlenbeck thinks it likely that a "multifactorial" combination of input both by the specific sensory channels (optic system, cochlear pathway, and spinobulbo-thalamic channels) *and* the nonspecific (activating) reticular channels are required for the maintenance of conscious cortical (cortico-thalamic) activities in the waking state (1954, p. 128–129; 1957, p. 186–187). An interesting case in point is one described by Adolf Strümpell in 1877. The patient had lost all contact with the outer world, as manifested by anesthesias, etc., except for integrity of input from the right eye and the left ear. Whenever that eye was covered and that ear plugged, she would fall into sleep within a few minutes.

The reticular activating substance is but a small part of the reticular substance, which Jules Déjérine described in detail at the turn of the century (1901) and which Paul Yakovlev referred to in functional terms in 1949 as a portion of the "innermost system of visceration", a concept which he recently expanded (1972). Déjérine

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Fig. 11. Joseph Jules Déjérine (1849–1917). Portrait by courtesy of Mme. le Docteur Sorrel-Déjérine, Paris, France.

observed that the reticular substance (his "formation réticulée"), nucleated in some parts of its domain, stretches far and wide: it occupies much of the inner core of the brain stem, extends up to the subthalamic and subpallidal regions, and insinuates itself into the thalamus.

According to Ramón-Moliner and Nauta (1966), Déjérine's reticular substance is made up of small neurons with long, rectilinear and sparsely arborizing dendrites subtending large and widely overlapping dendritic fields (hence neurons of the iso-dendritic type) that mingle freely with the fascicles of transit axons. Nauta and Haymaker (1969) propose that the hypothalamus be considered a component of the reticular substance. This concept may seem unorthodox, for the neuron pattern of the hypothalamus differs in some ways from that of the brain stem. But in parts of the medial portion of the hypothalamus, more specifically in its ventromedial nucleus, "excitation can spread from a given focus in any direction and can establish an in-