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EDITORIAL

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The history of Danish neuroscience

Abstract

The history of Danish neuroscience starts with an account of impressive contributions made at the 17th century. Thomas Bartholin was the first Danish neuroscientist, and his disciple Nicolaus Steno became internationally one of the most prominent neuroscientists in this period. From the start, Danish neuroscience was linked to clinical disciplines. This continued in the 19th and first half of the 20th centuries with new initiatives linking basic neuroscience to clinical neurology and psychiatry in the same scientific environment. Subsequently, from the middle of the 20th century, basic neuroscience was developing rapidly within the preclinical university sector. Clinical neuroscience continued and was even reinforced during this period with important translational research and a close co-operation between basic and clinical neuroscience. To distinguish 'history' from 'present time' is not easy, as many historical events continue in present time. Therefore, we decided to consider 'History' as new major scientific developments in Denmark, which were launched before the end of the 20th century. With this aim, scientists mentioned will have been born, with a few exceptions, no later than the early 1960s. However, we often refer to more recent publications in documenting the developments of initiatives launched before the end of the last century. In addition, several scientists have moved to Denmark after the beginning of the present century, and they certainly are contributing to the present status of Danish neuroscience—but, again, this is not the History of Danish neuroscience.

KEYWORDS

brain, Denmark, history, neuroscience, research, spinal cord

1 | PREFACE

The initiative for the present work was taken by the Lundbeck Foundation, which approached us proposing that we write an overview over the topic. The Lundbeck Foundation, the largest Danish foundation supporting neuroscience, had previously made an overview of present Danish neuroscience publications (Andersen et al., 2018) and was also inspired by the Federation of European Neuroscience Societies (FENS). FENS, through its History Committee, is interested in documenting the development of neuroscience in all its member states (https://www.fens.org/engagement/outreach/history-of-neuroscience). At the bi-annual FENS meetings, there are both lectures and exhibitions on the program. Finally, the FENS journal, the *European Journal of Neuroscience* (ENJ), has published some articles on the development of European neuroscience (Korpi et al., 2020; Lorusso et al., 2018). With this background, the Lundbeck Foundation contacted us regarding the possibility to write a chapter on the history of Danish neuroscience—possibly with a version published in the *EJN*. We have described the history from the beginning of neuroscience in Denmark. To distinguish *history* from *present time* is not easy, as many historical events continue in present time. Therefore, we have considered *history* as new major scientific developments in Denmark, which were launched before the end of the 20th century. With this aim, scientists mentioned will have been born, with a few exceptions, no later than the early 1960s. However, we often refer to more recent publications documenting the developments of initiatives launched before the end of the last century. Additionally, several scientists have moved to Denmark after the beginning of this century and certainly are contributing to the present status of Danish neuroscience—but, again, this is not the *history* of Danish neuroscience.

Many of the scientists mentioned have been so kind to guide us in their specific fields of research. We want to thank them for their assistance. A special thank should

be directed to Troels Kardel, Jesper Brandt Andersen, Tom Bolwig, Raben Rosenberg and Jens H. Henriksen for more extensive comments and suggestions.

2 | CHAPTER 1: THE EARLY PHASES OF NEUROSCIENCE DURING THE 17TH–19TH CENTURIES

2.1 | Thomas Bartholin

Danish Neuroscience dates back to the 17th century with **Thomas Bartholin** (1616–1680) and Nicolaus Steno (1638–1686). Thomas Bartholin was born in Copenhagen and came from an academic family with many scientific contributions and with influence at the University of Copenhagen (Olden-Jørgensen, 1992). Thus, his father Caspar Bartholin was also a professor and physician and studied human anatomy. Thomas Bartholin is mostly known for his contribution to the discovery of the lymphatic system, but he also made contributions to neuroscience (Andersen, 2017, 2018). He made the first description of the Sylvian fissure in the brain and gave it its name after his friend Franciscus Sylvius who had drawn his attention to the structure. Another neuroscientific contribution was through his opposing view of Descartes' theory of the pineal gland's major role as the seat of the soul, published in an anatomy book (Bartholin, 1651). Fourteen years later after Steno's careful studies on the pineal gland Descartes' theory finally vanished, see further below.

When the young Nicolaus Steno at the age of 18 started to study medicine at the University of Copenhagen, he chose Thomas Bartholin as tutor. Bartholin's role as tutor became significant. Throughout the years, they communicated with letters when Steno was abroad and Steno often wrote to Bartholin about his findings (Andersen, 2018, 2021).

2.2 | Nicolaus Steno

Nicolaus Steno (1638–1686) (Figure 1) was a multi-talented researcher contributing to anatomy, palaeontology, geology, and crystallography. He was born near Rundetårn (the Round Tower) in Copenhagen in Lutheran Denmark. He converted to Catholicism in his late 20s when he was a scientist associated with the Tuscan Grand Duke, Ferdinando II de' Medici in Florence. Three centuries after his death, in October 1988, he was beatified by Pope John Paul II (Andersen, 2018, 2021; Anzai et al., 2014; Gotfredsen, 1950; Kardel & Maquet, 2018a; Moe, 1994; Rafaelsen, 1986; Sténon & Andrault, 2009).

FIGURE 1 Nicolaus Steno. Painted by J. P. Trap in 1868. With permission from the University of Copenhagen.

He made his first contribution to anatomy during doctoral studies in Leiden in the Netherlands, when demonstrating that saliva is secreted to the mouth from the parotid gland through a duct soon named after him, the ductus parotideus stenonianus. Thereby, the parotid structure, well known from swelling in mumps, got a function as a gland, contradicting assumptions that saliva originated from the gullet (Descartes) or the brain. Subsequently, he discovered the lacrimal ducts and suggested that tears were secreted by tiny glands and not the brain (Andersen, 2021; Kardel & Maquet, 2018c).

Later, he proposed that muscles shorten when fibres shorten. He drew on inspiration from his friend Jan Swammerdam who had observed that the muscular volume did not change when the muscle contracts. He was further inspired from Galileo and used Euclid's Elements in a geometric model of muscle contraction, among the first applications of mathematics in biology. That muscle fibres shorten seems trivial nowadays. However, in those days, it was incompatible with the classical theory based on an Aristotelean axiom of inflation of the muscle, by 'spiritus animalis' (from the

brain through the nerves), causing the contraction. Stensen's model for fibre shortening was accepted by Bartholin, but first generally accepted in the next century when observed by microscopy (Andersen, 2021; Andrault, 2010; Castel-Branco & Kardel, 2022; Kardel, 1994, 2008, 2021).

A remarkable neuropathological study was his dissection of the brain of a calf with hydrocephalus in Innsbruck in 1669. The head was markedly enlarged, and the lateral and third ventricles were merged into one big cavity, 'The water tasted salty and had a reddish colour as is usual for all these serositis which have been retained in the inner cavities of animals for some length of time. This liquid weighed 4 lb. It had expanded the cavities of the brain to such an extent that much time was spent "searching for the brain inside the brain itself". The skull was very similar to a "hollow pumpkin"' (Kardel & Maquet, 2018b). Steno described in detail a list of abnormalities but also that the brainstem had not yielded to pressure from the water inside the skull. Still the calf had been able to live and somehow sense for some weeks (Andersen, 2021; Gjerris & Snorrason, 1992; Kardel & Maquet, 2018b).

One of Steno's main contributions to neuroscience was related to the investigation of the anatomy of the pineal gland. Descartes had proposed and illustrated how the pineal gland was the seat of the soul, acting by rotation to distribute animal spirits through the brain's ventricles to brain tissue and along the nerves to the muscles, thereby causing them to swell and shorten. Steno in his careful studies demonstrated that the pineal gland was merely grey matter with black spots, being fixed to the surroundings and thus immobile. The discussion was quite sophisticated, Descartes assuming that the vessels around the gland were arteries supplying energy versus Steno showing that it was just veins (Andersen, 2021; Kardel & Maquet, 2018a).

In a lecture on the Anatomy of the Brain given in 1665 to a learned assembly in Melchisedech Thévenot's home in Paris, Steno outlined a new programme for methods in research of the brain with critique of Descartes, Thomas Willis and others and of unfounded localisation of mental faculties to distinct parts of the brain having been proposed by Willis. The lecture was published in 1669 and subsequently translated to several languages (Maquet, 2018; Scherz, 1965).

Steno's brain research and myology were a combined investigation of the brain's motor control effectuated by the skeletal muscles (Kardel, 2008). As royal anatomist in Copenhagen, Steno on 29 January 1673 in the opening lecture, the 'Prooemium demonstrationum anatomicarum', distinguished what is not known from the little we know or can see: 'Beautiful is what we see, more beautiful what we know, but by far the most beautiful is what we do not know' (Kardel & Maquet, 2018d; Steno, 1675).

Steno's research activities outside the area of anatomy and neuroscience were also impressive and included earth science and history with studies of geological layers (stratigraphy), fossils (palaeontology), of crystal growth (crystologtaphy) and of rock cycles as well as the use of mathematics in his research as a natural scientist. The aspects have been gathered in a special issue of Substantia (Dominici & Rosenberg, 2021).

2.3 | Jacob Benignus Winsløw

A major Danish contribution to neuroscience came in the 18th century from **Jacob Benignus Winsløw** (1669–1760). Born in Odense and a great-nephew of Nicolaus Steno, he was educated as physician in Copenhagen. Aged 27, he left Denmark in the winter of 1697 to commence a study travel in Europe. He spent his first year at the University in Leiden before moving on to Paris to stay there for the rest of his life. Like his great-uncle, Winsløw converted to Catholicism. He had been supported by a grant from Denmark, which was lost when converting. However, he soon integrated in the French system. In 1743, he was appointed as Professor anatomicus at Jardin du Roi. He was a remarkable anatomist dealing with investigation of details of the human body's organs related with function. His textbook *Exposition Anatomique de la Structure du Corps Humain* was published in several languages and appeared in altogether 29 editions throughout 1732–1775. He investigated muscle function in relation to torticollis, brain structures in relation to motor function and the sympathetic ganglia in relation to gastrointestinal function. In his later years, he published a book on the definite signs of death as a safeguard against 'apparent death', an interest he had had since his youth. An article on this topic was also translated into several languages (Maar, 1912; Saad, 2021; Snorrason, 1969).

3 | CHAPTER 2: THE CLINICAL DISCIPLINES IN THE 19TH AND FIRST HALF OF THE 20TH CENTURY

Danish neuroscience has from its very beginning been closely linked to clinical science. Thus, Thomas Bartolini, Nicolaus Steno and Jacob Benignus Winsløw described

above were all physicians with inspiration from clinical settings.

In the 19th and first half of the 20th centuries, essentially all Danish neuroscientific activities took place in the clinical environments. The environment for both research and patient care expanded considerably in the 19th century and continued to do so in the subsequent century.

Thus, the first regular psychiatric hospital in Denmark was established when the municipality of Copenhagen built Sankt Hans Hospital situated 30 km west of Copenhagen in 1808–1816. The hospital has remained a main player in clinical and basic neuroscience throughout the years (Fog, 1995; Møllerhøj & Kragh, 2018).

By the end of the 19th century, the core of Danish psychiatry, including neurology and neuroscience, was at *Kommunehospitalet* in Copenhagen, established in 1875 (Kragh, 2008b).

In 1910, the royal Frederik's Hospital, belonging to the state of Denmark, was moved to a new campus in what in those days were the suburbs of Copenhagen—today next to downtown. The name was Rigshospitalet, and in 1913, the first Danish Department of Neurology was established at this location. A book about the department was published at its 100-year anniversary (Paulson, Thage, & Waldemar, 2013). Neurology was now, from 1913 separated from psychiatry. Today Rigshospitalet is the main Copenhagen University Hospital with extensive research activities.

3.1 | Individual scientists from the period

3.1.1 | Carl Lange

Carl Lange (1834–1900) was a remarkable person and brilliant scientist. As a physician, he was both a psychiatrist and a neurologist. He spent a couple of years studying histology and physiology in Zürich and Firenze. He became professor (of pathology) at the University of Copenhagen in 1885 and was active in politics, a member of Copenhagen's Town Council (Lund, 1991; Schioldann, 2011; Snorrason, 1973).

Lange's early research was in the field of neurology, and Danish clinical neuroscience dates back to Lange's description of aphasia and bulbar paralysis (Lange, 1868); his main neurological contributions dealt with spinal diseases, especially syphilitic meningitis (Lange, 1872). Lange's contribution to psychiatry is remarkable (Amdisen, 1985; Mellergård, 2007; Schioldann, 2011). In 1885, he published in Danish *On Emotions - Psycho-Physiological Study (translated)* (Lange, 1885). It was later translated into German, French and English (Lange, 1967). He advocated that emotions are physiological reflex mechanisms rather than primary psychological experiences. The theory is known as the James–Lange theory after William James who reached similar conclusions in 1884. A year after his work on emotions, he published his theory on periodical depression, also in Danish, translated: *On Periodical Depressions and their Pathogenesis* (Lange, 1886). The work was soon translated into German, and much later, at the beginning of the new millennium, into English. The description corresponds to what we today would call 'major depressive disorder without mania'. His observations and theories led to the use of lithium for the treatment of depression. The treatment with lithium was at that time not used widely and was abandoned. However, more than half a century later, new theories led to the use of lithium for the treatment of major depression and was introduced by the Danish physicians Erik Strömgren and Mogens Schou as described below.

The interest in neurology and neuroscience grew in Denmark in the later part of the 19th century, and several young physicians had been inspired by Carl Lange. Many of the activities were gathered at the Department of Psychiatry at Kommunehospitalet in Copenhagen. Neurology was also included in the department.

3.1.2 | Alexander Friedenreich

Alexander Friedenreich (1849–1932), a disciple of Carl Lange, became chief of the Department of Psychiatry at Kommunehospitalet in Copenhagen (1998–1920) and Denmark's first professor of psychiatry (1916–1919) (Schmidt, 2011). He was as much a neurologist as a psychiatrist. He wrote his thesis on athetosis, stressed the importance of emotions in psychiatry, wrote a textbook in psychiatry (Friedenreich, 1901) and the first Danish textbook in neurology (Friedenreich, 1882).

Friedenreich had a strong desire to strengthen biological psychiatry. Fortunately, this coincided with the University of Copenhagen's need to strengthen the limited teaching in psychiatry, which had started in 1868. Thus, the University had to negotiate with Friedenreich in order to engage him more in teaching. The outcome was remarkable and resulted in the establishment in 1898 of a basic scientific university department, *Psychiatry Laboratory* at Kommunehospitalet, headed by the chairman of the Department of Psychiatry, that is, Friedenreich. This

was a milestone in hospital academic research, and the unit is still active more than 100 years later (Mellerup et al., 1998). The university had been somewhat reluctant to establish a laboratory in a hospital environment located 'far away' (1 km) from the university campus.

3.1.3 | Asmus Julius Thomsen

A particular discovery in Danish neurology was done by the district physician and medical advisor **Asmus Julius Thomsen** (1815–1896, Schleswig, Denmark; after 1864 Germany) at the time when Danish neurology was established. In 1876, he was the first to describe the genetic neurological disease, congenital myotonia, based on observations in himself and his family (Thomsen, 1876). The name Thomsen's disease was proposed in 1883 by Karl Friedrich Otto Westphal.

3.1.4 | August N. M. Wimmer

August N. M. Wimmer (1872–1937) became the director of the psychiatric hospital Sankt Hans Hospital in 1912. He had a major impact on the evolution of the hospital, and major contributions to psychiatric research were made (Kragh, 2008b). After Friedenreich's retirement in 1920, Wimmer took over the position as chief of Department of Psychiatry at Kommunehospitalet. In 1933, a Department of Psychiatry was established at Rigshospitalet, the main university hospital in Copenhagen. Wimmer became chairman of the department, and his professorship was moved to Rigshospitalet. The Psychiatric Laboratory at Kommunehospitalet discussed below under 'Neuropathology' also moved to Rigshospitalet. Wimmer had a broad research activity and wrote many papers within the area of neuropsychiatry (organic background for psychoses, including neuroinfections). His and his fellows' work on *encephalitis lethargica* are classical milestones (Wimmer, 1924). Wimmer's main contribution was his work on psychogenic psychosis, which became internationally renowned. 'Evolutive Paranoia' is among his first publications and later translated to English (Berrios et al., 2018; Schioldann, 2019). His work published in Danish, *Psychogenic Forms of Mental Diseases*, is the first comprehensive account of the reactive psychoses. His textbook in Danish from 1936, *Special Clinical Psychiatry*, covered his views on psychiatry, partly based on his own observations. The book became a standard work in clinical psychiatry. Wimmer attracted younger physicians both to psychiatry and neurology, and he remains one of the most important clinical grand old men in Danish neuroscience (Kragh, 2008b; Ostenfeld, 2011a).

3.1.5 | Erik Strömgren

Erik Strömgren (1909–1993) was a pioneer of psychiatric epidemiology as well as of lithium treatment for depression. He was inspired by Bruno Schulz from Munich. He gained part of his training with Wimmer with whom he conducted his ground-breaking genetic-epidemiological studies on the island Bornholm in 1935, published in German in 1938, and with later follow-up in 1983 (Bøjholm & Strömgren, 1989). He moved to Aarhus in 1943 where he became chief of the Department of Psychiatry, Risskov, and professor in psychiatry at the University of Aarhus in 1945. Strömgren created a rich environment for clinical practice and research—most famously the institutes for genetics and epidemiology—and for biological psychiatry with a world-famous unit for lithium research to be headed by Mogens Schou (see below). Strömgren's contributions earned him a well-deserved reputation as a European leader in psychiatry as described in many articles (Berrios & Schioldann, 2017; Bertelsen, 2009; Kragh, 2008b; Schioldann, 2014; Steinberg et al., 2011; Vestergaard, 2011) including one with his wife as co-author (Schioldann & Stromgren, 1996).

3.1.6 | Mogens Schou

Mogens Schou (1918–2005) specialised in clinical chemistry, held a research position from 1965 in Aarhus and was appointed professor of biological psychiatry in 1971 at the Psychiatric Hospital in Risskov, Aarhus (Grof & Müller-Oerlinghausen, 2018). Schou's research interests focused on the therapeutic uses *of lithium for* patients with mood disorders, research he had initiated together with Strömgren (Schou et al., 1954). Carl Lange's ideas about lithium (see above) half a century earlier was by then forgotten. But, after the discovery in 1949 by John Cade in Australia of lithium's effect on mania, Schou and Poul Christian Baastrup set out to describe lithium's prophylactic effect in bipolar disorder, and they published a number of investigations using double-blind trial of prospective-discontinuation design and with random allocation of manic-depressive (bipolar) patients (already on lithium) to lithium or placebo. Their hypothesis was confirmed and was published in *The Lancet* in 1970 (Baastrup et al., 1970; Schou, 1997). These world-famous studies were a major contribution to treating and preventing bipolar disorders, and despite severe

criticism at the time of the publications, the efficacy of lithium treatment is no longer disputed.

3.1.7 | Knud Haraldsen Krabbe

Knud Haraldsen Krabbe (1885–1965) became chairman of Neurology at Kommunehospitalet, Copenhagen, in 1933 when the Department of Psychiatry was split up in the Departments of Neurology and Psychiatry (Ostenfeld, 2011d). Krabbe described already in 1916, a genetic neurological disease, globoid cell leukodystrophy or galactosylceramide lipidosis (Krabbe, 1916). Later the disease was named Krabbe's disease or Krabbe's leukodystrophy. Both Thomsen's and Krabbe's diseases are now described in all international textbooks of neurology.

3.1.8 | Mogens Fog

Mogens Fog (1904–1990) was Chairman of the Department of Neurology at Rigshospitalet and professor of neurology at the University of Copenhagen. Fog had his scientific inspiration from basic science and made remarkable studies on the cerebral circulation in response to changes in blood pressure (Fog, 1938); see further later in this article. He also contributed with clinical studies, for example, on the pathogenesis of Schadler's disease (Christensen & Fog, 1955). Fog's scientific contribution was soon reduced as a consequence of the Second World War. During the war, he was thus active in the resistance movement, late in the war taken prisoner by the Germans and made a remarkable escape. After the war he was minister in the first government. Thereafter, he returned to neurology as a leading person, had many important positions of trust and ended his career as Vice Chancellor of the University of Copenhagen (Møller, 2009a, 2009b).

3.2 | Copenhagen University's Psychiatric Laboratory and Neuropathology

As mentioned above, Alexander Friedenreich had a strong desire to strengthen biological psychiatry, and he managed to establish a university department in the frame of the clinical department of psychiatry, the Psychiatric Laboratory at Kommunehospitalet. The unit became the frame for a broad spectrum of neuroscience and had a key role in the establishment of neuropathology.

August Wimmer (mentioned above) and other scientists did their research in the laboratory in their young years, on Nissl staining and on neurofibril staining of the cerebral cortex. In this context, it should also be mentioned that the first female chief physician in the municipality of Copenhagen, Gudrun Brun, wrote her thesis (1940) on serum lipids in manic-depressive patients at the Psychiatric Laboratory. In 1913, **Axel Valdemar Neel** (1878–1952) became a research assistant and leader of the Psychiatric Laboratory, a position he held until his retirement in 1948. Neel was a kind of a lonely rider as he wrote about 120 scientific publications, and he was the sole author of approximately 100 of these. Under Neel's leadership, the research activities in the laboratory also got a broader frame, and studies now included diffuse sclerosis, brain tumours, encephalitis and cerebrospinal fluid (CSF). He also wrote an article on the history of dementia paralytica with special emphasis on Scandinavian contributions (Mellerup et al., 1998; Neel & Ostenfeld, 1946). He described with his colleague J. Bing the rare Bing–Neel syndrome, a condition with hyperglobulinaemia affecting the central nervous system (CNS) (Bing & Neel, 1936). In the late 1930s, collaboration was established among others with Erik Strömgren mentioned above (Ostenfeld, 2011b; Strömgren, 1952).

Already in 1935, 1 year after neurosurgery was established at the Department of Neurology at Rigshospitalet, the chief of neurosurgery Eduard Busch who himself had interest and knowledge in neuropathology decided to reinforce the field. The young physician, **Erna Ingeborg Christensen** (1906–1967) became the grand old lady of Danish neuropathology. She wrote her thesis on chronic subdural hematoma, and during the coming years, her research activities covered several fields of neuropathology. She succeeded Neel in 1948 as chief of the Psychiatric Laboratory of the University of Copenhagen (Klinken, 2000; Ostenfeld, 2011c; Willadsen, n.d.). Neuropathology was now established in Denmark in the frame of a university department hosted in a department of clinical psychiatry. For many years, the laboratory at Rigshospitalet served all of Denmark with neuropathology. Erna Christensen educated essentially the whole next generation of neuropathologists in Denmark.

The Psychiatric Laboratory of the University of Copenhagen had always had a broad research activity with somewhat sparse relation to psychiatric topics. This became even more evident under the leadership of

Christensen who with great success reinforced neuropathology. After her death in 1967, the organisation changed, and the Psychiatric Laboratory became the *Psychochemistry Institute* in 1968 under Ole Jørgen Rafaelsen's leadership. In 1990, the Psychochemistry Institute was renamed to the Laboratory of Neuropsychiatry (Mellerup et al., 1998), and neuropathology was developed separately as described in Chapter 3 in the section on Neuropathology.

4 | CHAPTER 3: THE EVOLUTION OF CLINICAL NEUROSCIENCE IN THE SECOND PART OF THE 20TH AND BEGINNING OF 21ST CENTURY CHAPTER 3 – THE EVOLUTION OF CLINICAL NEUROSCIENCE IN THE SECOND PART OF THE 20TH AND BEGINNING OF 21ST CENTURY

In the 20th century, and especially in the latter part of it, neuroscience is growing in Denmark and continues to grow in the 21st century. New research areas and new research groups are established. As mentioned in the previous chapters, most Danish neuroscience had hitherto more or less been linked to research with clinical background or activities. Now new groups and activities in basic neuroscience are growing in the universities' basic scientific environment. Still neuroscience in the clinical environment is also reinforced and achieved new milestones. Consequently, we have divided our description of this evolution and its scientific achievements in two parts, one related to the clinical research primarily taking place in the university hospitals and one primarily taking place at the universities' basic scientific departments (see Chapter 4), although much translational research causes overlap to be present.

In psychiatry, neurology and other fields of clinical neuroscience, new trends take place in the second half of the 20th century—*a new epoch starts*. New neuroscience environments are established, linking clinical function with research and education much more than hitherto seen. These environments attracted several talented young physicians, of whom many became the coming leaders in their fields.

In the present chapter, we describe this evolution the start of the new epoch and how it formed the basis for the establishment of new focus areas with new scientific achievements. Sub-specialisation took place when expansion became possible at the end or the 20th century and beginning of the present.

We introduce the chapter with a brief introduction of the new epoch followed by a more extensive description of the new specialty, 'Clinical Physiology', with Niels A. Lassen as one of the foremost leaders. He had a tremendous influence on the evolution of Danish neurology and neuroscience. Finally, we describe milestones in other fields of psychiatric and clinical neuroscience research.

The start of a new epoch

The beginning of the second half of the 20th century was exceptional with a severe poliomyelitis epidemic in 1952 and 1953. Thousands were affected, mostly children and youngsters. The most important and serious symptom of poliomyelitis is due to the involvement of motor neurons, resulting in severe flaccid asymmetric paresis, which often affects respiration. About 15% of the patients had breathing difficulties. At the peak of the epidemic, more than 300 patients needed assistance with respiration at Blegdamshospitalet in Copenhagen, the main hospital for treatment of poliomyelitis. Already in 1950, WHO had established an anaesthesiology centre in Copenhagen. Under the leadership of **Henry C. A. Lassen** (1900–1974), father of Niels A. Lassen (mentioned in subsequent parts of the review), the 'Copenhagen Epidemic' became a milestone in the development of modern intensive therapy (Lassen, 1953). In those days, respirators were few and built as external devices that you put the patient into or applied externally over the patient's chest. This milestone was reached when **Bjørn Ibsen** (1915–2007) and colleagues introduced tracheostomy and continuous manual ventilation carried out by young medical students—mortality dropped by 50%–75% (Ibsen, 1954).

In the frame of the poliomyelitis epidemic, a young physician, **Erik Skinhøj** (1918–1983), investigated the clinical course of poliomyelitis and wrote his doctoral thesis 'Some problems of acute anterior poliomyelitis and its sequelae' (Skinhøj, 1949). He specialised in neurology, became chief of neurology at Bispebjerg hospital in Copenhagen and established a broad collaboration with Niels A. Lassen who had a wide international neuroscientific network (see later in this chapter). Together, they attracted and educated a new generation of young physicians who obtained part of their education abroad and became coming leaders in neurology. This constituted the basis for a new milestone in Danish neurology. Skinhøj later in the mid-1970s succeeded Fog as chairman and professor of neurology at Rigshospitalet and became Vice Chancellor of the University of Copenhagen some years later. Skinhøj's main contribution to science and neurology started in the 1960s with studies of cerebral blood flow (CBF) in collaboration with Niels A. Lassen; see later in this chapter. Among Skinhøj's achievements was the first description of focal flow

reduction during attacks of migraine with aura (Skinhoj & Paulson, 1969). After Skinhøj became Vice Chancellor, Olaf Paulson took over the leadership of the department and continued the collaboration with Lassen.

In psychiatry, the development in 1950 of chlorpromazine, the first antipsychotic drug, was an important achievement with major impact on clinical psychiatry. Biological psychiatry became a focus area. In this context, **Ole Jørgen Rafaelsen** (1930–1987) established a frame linking the more traditional psychiatry to the area of biological psychiatry. He graduated in 1953 and specialised first in internal medicine, then in psychiatry. His first postgraduate training was in Aarhus. Here he wrote his doctoral thesis, a review on the direct effect of insulin on the CNS (Rafaelsen, 1961). In 1961–1962, Rafaelsen was research fellow at Peter Bent Brigham Hospital in Boston where he continued his studies of insulin, now on the diaphragm and adipose tissue (Rafaelsen et al., 1965). He returned to Copenhagen to continue his training, and from 1965 to 1972, Rafaelsen worked at Rigshospitalet in Copenhagen as senior resident registrar in psychiatry. Here he participated in the reorganisation of the University's Psychiatric Laboratory (see below) and reorganised it as the University's Psychochemistry Institute with a metabolic ward for the investigation of the biochemistry of affective disorders. From 1972 until his untimely death in 1987, he was professor of psychiatry at the University of Copenhagen. His research in these years dealt, for example, with rating scale for depression, now widely used (Bech et al., 1986), nocturnal temperature in affective disorder in relation to treatment with lithium (Avery et al., 1982) and catecholamines in the CSF in depressed patients (Christensen et al., 1980). In 1983, Rafaelsen was appointed President of Collegium Internationale Neuro-Psychopharmacology. However, for Danish neuroscience, it is even more important that he created a new epoch in psychiatry, an environment attracting many talented young scientists who established collaboration and became coming leaders in both psychiatry and other disciplines (Bech & Mellerup, 2007).

In Aarhus, the new epoch in clinical neuroscience started somewhat later, in the 1980s and augmented further in the 1990s. In this context, Palle Juul-Jensen (1929–1998) should be mentioned. His background was in clinical neurophysiology. He wrote his DMSc thesis in 1963 on clinical and social aspects in epilepsy (Juul-Jensen, 1963). Later, as research fellow in neurology in 1965–1966 at Harvard Medical School, Boston, he completed a study with Derek Denny-Brown on the multifactorial cause of epilepsia partialis continua (Juul-Jensen & Brown, 1966). Subsequently, his own research achievement suffered from important administrative and positions of trust engagements. Among the activities, he was Dean of the Faculty of Medicine at the University of Aarhus for 17 years in a row (Snorrason & Harding, 2015). Juul-Jensen supported younger physicians and encouraged them to seek part of their education in other departments in Denmark and abroad. Thereby, directly or indirectly, a new generation of talented academic neurologists with main scientific interest was created in Aarhus. Among these were Johannes Jakobsen, Troels Staehelin Jensen and Flemming Bach, all mentioned below.

In psychiatry in Aarhus, Mogens Schou's research in biological psychiatry as described in the previous chapter created the foundation for a strong scientific environment, which formed the basis for the new epoch.

At the 100-year anniversary of the Danish Neurological Society, a book on the history of the society was published (Therkelsen, 2000). The book contains a list of Danish 'neuro' doctoral theses (MDSci; more extensive than PhD thesis) from the 20th century, total 297, reflecting a widespread activity in many hospitals and institutions (Kardel & Boysen, 2000). A previous publication by the same authors listed all the theses back to the 17th century (Boysen & Kardel, 1992).

4.1 | Neuroscience within clinical physiology: A main player in Danish neuroscience

In this section, we describe the new field clinical physiology as pioneered by Lassen and Munch and its evolution with many new initiatives and new research groups. The important field of classical clinical neurophysiology dealing with electrophysiological events in the brain and muscles and pioneered by *Fritz Buchthal* is described in a separate section later in this and the next chapter.

The new field, clinical physiology, was established in Denmark in the beginning of the 1960s by the pioneers **Niels Alexander Lassen** (1926–1997) and **Ole Munch** (1926–2002). Thus, the first departments of clinical physiology in Denmark opened at Bispebjerg Hospital (1962) and Glostrup Hospital (1963) with Lassen and Munch, respectively, as leaders. They had worked together and introduced the use of radioisotopes for blood flow measurements, first in the brain (Lassen & Munck, 1955) and later also in other organs. They were new types of leaders attracting young talented persons to join their research and thereby establishing collaborations and strong research groups.

Lassen established a collaboration with the neurologist Erik Skinhøj as mentioned above, and their disciples became the foremost coming leaders in neurology in the eastern part of Denmark. Lassen is considered one of the greatest neuroscientists in Denmark. As a consequence,

the present section is more extensive than most other parts of our report.

Neuroscience in clinical physiology was not restricted to Lassen's department, but became gradually established in other hospital units including laboratories in clinical departments in neuro-disciplines and psychiatry. These initiatives and scientific achievements are gathered in the following part of this chapter.

Before proceeding, we will give a short introduction on parts of the history of the scientific background for clinical physiology in neuroscience.

4.1.1 | The background for neuroscience in clinical physiology

Neuroscience in the 20th century in Denmark made remarkable contributions to research in the fields of capillary physiology, blood–brain barrier (BBB) transfer and CBF studies paving the way for new insights into neurophysiology, cognitive psychology and pathophysiology of cerebral diseases. **August Krogh** (1874–1949) made renowned contributions to the anatomy and physiology of capillaries. In muscle, capillaries, which are closed in the resting state, open during exercise increasing blood flow and effective capillary surface area allowing for sufficient oxygen to diffuse into the exercising muscle. He was honoured with the Nobel Prize in Physiology and Medicine in 1920 (Larsen, 1998).

Valdemar Henriques (1864–1936) in 1913 published the first results on blood flow measurements using a single injection of a chemical substance (Henriksen, 2007). Inspired by Henriques, **Mogens Fog** (1904–1990) in the 1930s studied the cerebral circulation in response to modulation of arterial blood and intracranial pressure. Fog observed as the first that the pial arterioles on the surface of the brain dilate in response to intracranial pressure increase (Fog, 1933). He further observed that the arterioles constricted in response to blood pressure increase and dilated in response to pressure decrease (Fog, 1938). These observations fully agree with later studies of CBF showing that flow remains constant within wide limits of blood (and intracranial) pressure variations—the so-called autoregulation of CBF. Fog's contribution to Danish neuroscience is also described in the previous chapter on neuroscience in the 19th and beginning of the 20th centuries.

In the second half or the 20th century, neuroscience was in many respects reinforced in Denmark. In the field of blood–brain transfer and cerebral circulation, two persons had major impact: **Ulrik Christian Crone** and **Niels Alexander Lassen**, both born in 1926 (Henriksen, 2018). Crone's research is described in the later chapter, Lassen's below. They were both MDs and had to a limited extent worked together. However, they had two rather different personalities. Crone was a basic scientist and professor at the Department of Physiology at the University of Copenhagen. His studies were performed in experimental animals. He regarded experimental studies as superior to clinical and never attempted translating experimental to clinical neuroscience. The barrier to clinical research was rather evident. Thus, a young fellow (one of the authors, OBP) had just graduated as a physician. As a senior student, he taught younger students physiology and considered pursuing a career in basic physiology. After graduating as MD, however, he got the idea to start his postgraduate career with a small project in clinical physiology with Niels Lassen. When he told Crone about his thoughts, he was kindly advised that it was not sure there would be a way back to basic science for him. Lassen, being more open minded, considered good science to be science with impact in the field and independent of whether it came from experimental studies in animals or from human investigation. He established, as mentioned, the discipline clinical physiology in the hospital settings and became the first professor in this field in Copenhagen.

4.1.2 | Niels Alexander Lassen's research

Niels Alexander Lassen (1926–1997) (Figure 2) was born and grew up in Copenhagen. He was a brilliant physiologist and became one of the most renowned neuroscientists in Denmark, perhaps the greatest since Nicolaus Steno (Henriksen, 2018; Henriksen et al., 1997; Henriksen & Lassen, 2019; Paulson, 2000; Paulson, Henriksen, & Parving, 2013). In a recent interview with Marcus Raichle on his research, Lassen is discussed as a leading and inspiring figure in the field (Muhlert, 2021). Shortly after he graduated as physician from the University of Copenhagen, he started his research career. Together with his classmate from high school and during his studies of medicine, Ole Munck, they explored on their own the possibility of studying blood flow using radio-labelled inert gases. In the United States, Kety and Schmidt had in the late 1940s introduced the inert gas nitro-oxide for measurement of CBF. Lassen and Munck used instead the radioactive isotope ^{85}krypton, which improved the method considerably, both in terms of accuracy and technical execution (Lassen & Munck, 1955). Among others, they demonstrated as the first a side-to-side difference in the CBF (Munck & Lassen, 1957). In 1957, Lassen went to Seymour Kety's laboratory at NIH, USA, and stayed there for a little more than 1 year. He repeated and expanded the studies on the use of ^{85}krypton in CBF measurement, and the world

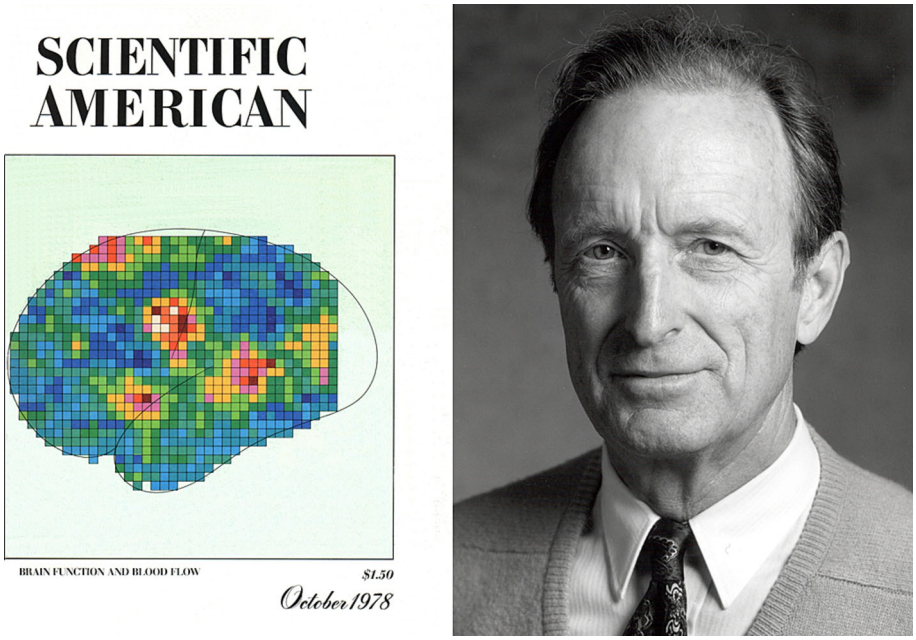

FIGURE 2 Niels Alexander Lassen. Left: Cover from Scientific American from 1978 illustrating unctional activation (yellow/read areas) when reading aloud. Right: Niels A. Lassen around 1990. Photo by Rigmor Mydtskov.

was now convinced of a new milestone in brain research. During his stay at NIH, he wrote his classical review article on CBF and oxygen consumption in man published in 1959 in *Physiological Reviews* (Lassen, 1959). CBF research remained Niels Alexander Lassen's main research field throughout his life.

In the late 1950s, Lassen met David H. Ingvar from Lund, Sweden. They started a collaboration and became close friends. Their idea was to further develop the radioactive inert gas technique in order to measure the regional cerebral blood flow (rCBF). The limitation of the Kety Schmidt method was that only global (or predominantly one hemisphere) CBF could be calculated, as tracer measurements took place from the arterial inflow and the jugular venous outflow from the brain. Lassen and Ingvar now introduced the intra-arterial injection method. ^{85}Krypton was injected into the carotid artery, and the uptake and clearance of ^{85}krypton was measured by a Geiger–Müller detector placed over the exposed cerebral cortex in cats (Lassen & Ingvar, 1961). Soon the method was introduced in man, now using the gamma emission instead of beta emission of ^{85}krypton and later of ^{133}Xe, allowing for detection of the radioactivity with externally placed scintillation detectors.

With the development of the intra-arterial ^{133}xenon injection method for CBF recording and the ultimate construction of a 254-detector system, the basis was established for a brand-new field in brain research—brain mapping of cerebral function. Lassen and Ingvar can indeed be considered the fathers of functional brain mapping, and the review article in *Scientific American* remains a classic milestone (Figure 2) (Lassen et al., 1978). The field has since expanded and is nowadays performed with positron emission tomography (PET) and even more with functional magnetic resonance imaging (fMRI).

The 254-detector system for measurement of CBF using intracarotid ^{133}xenon injection was introduced approximately at the same time as the computed tomography (CT) scanner. The CT scanner resulted in a major revolution in diagnostic neuroradiology. Carotid angiography which to a vast extent had been the first choice of neuroradiological investigation was rapidly replaced by the atraumatic CT scans. Still in Denmark, the capacity was very limited until around 1980. As many of the blood flow studies had been made in conjunction with cerebral angiograms, this method had also to be revised and become less traumatic. Consequently, Lassen went ahead with the company MediMatic and constructed a dynamic single-photon emission computed tomography (SPECT) scanner allowing to follow the rapid uptake and washout of inhaled ^{133}xenon (Stokely et al., 1980). The SPECT scanner not only gave possibilities to continue CBF research but further opened for a new dimension of research possibilities. The scanner was in use for the next two decades and gave rise to hundreds of publications (Lassen et al., 2021). The SPECT scanner also allowed for the use of new isotopes for blood flow measurements such as ^{99m}Tc-HMPAO, a radiolabelled compound that is lipophilic crossing the BBB, but thereafter rapidly transferred to a hydrophilic substance, which is trapped in the brain. Indeed, the first clinical studies with ^{99m}Tc-HMPAO were performed with this SPECT scanner (Andersen et al., 1986). This compound made blood flow

studies possible when the subject was outside the scanner, for example, in the patients with epilepsy, ^{99m}Tc-HMPAO could be injected during the seizure, and the patient scanned a couple of hours later in a calm environment. The ^{99m}Tc-HMPAO distribution would still reflect the flow, just after the injection when the patient had the seizure.

Not only did Lassen develop a new method for measurements of CBF, but he also applied them for extensive physiological research. Some highlights and milestones should be mentioned. His article in *The Lancet* in 1966, 'Luxury perfusion syndrome and its possible relation to actual metabolic acidosis localised within the brain', is a discussion with new ideas and theories on the role of tissue acidosis, perfusion changes and flow surpassing the metabolic demand (Lassen, 1966). The article gave rise to many thoughts and studies during the coming years, for example, in patients with stroke where regional flow was measured with the intra-arterial ^{133}xenon injection method (Hoedt-Rasmussen et al., 1967). The term 'steal' syndrome was introduced. The steal syndrome implies that a vasodilator stimulus causes a normal flow increase in healthy tissue, resulting in a paradoxical flow decrease, a steal, in the ischaemic or borderline ischaemic tissue where vessels already are dilated. The steal syndrome was further stressed in the 1980s in patients with threatening ischaemia as a consequence of carotid artery occlusion or severe stenosis (Vorstrup et al., 1984). Other achievements dealt with studies on CBF autoregulation (flow is independent of blood pressure within wide physiological limits under normal conditions) (Strandgaard et al., 1974) and studies of migraine showing that migraine with aura is followed by spreading flow reduction in the cerebral cortex (Lauritzen et al., 1983a). As mentioned above, studies of functional activation were a main goal in Lassen's research. A notable example from his later years is his collaboration with his Japanese colleague Iwao Kanno on activation when reading syllabograms in the Japanese language (Law et al., 1991).

Lassen was also active in other areas of neuroscience. He adapted the double indicator dilution method for use in man. The method was originally introduced by Crone for studies of the BBB in dogs; see further Chapter 4. Lassen and co-workers demonstrated intravascular separation of the transit not only for red cells and plasma but also for smaller and larger molecules (Lassen et al., 1971). The method was since used by his disciples for a series of studies as described later in this chapter.

Lassen was an excellent mathematician, reflected in many of his publications. Together with William Perl, he wrote the renowned classical book *Tracer Kinetic Methods in Medical Physiology* (Lassen & Perl, 1979). In his last decade, his research activities dealt as well with neuroreceptors, especially the benzodiazepine receptors using predominantly PET and SPECT (Lassen et al., 1995), and introduced the so-called Lassen plot, which still remains classic (Lassen, 1992).

4.1.3 | Further development in the field of neuroscience in clinical physiology

In the early 1970s, **Tom Bolwig** (1937–) started to build a laboratory for experimental studies in rats in the frame of the Department of Psychiatry at Rigshospitalet. The laboratory continued in the 1980s and 1990s as a common laboratory with the department of neurology headed by Olaf Paulson. It is now part of the Neurobiology Research Unit at Rigshospitalet. Tom Bolwig became later and in 1982 professor of psychiatry at Rigshospitalet, Copenhagen.

Among Bolwig's early studies, one solved the debate on whether lactate is produced in the brain during seizures when the blood is sufficiently oxygenised. Lactate is rapidly metabolised when oxygen is present, also postmortem, making it difficult to perform rapid measurements. The problem was solved with the contribution of Bjørn Quistorff who made an ultra-rapid cutting-freezing technique for rat brains, and the presence of lactate was demonstrated during electroconvulsive seizures (Bolwig & Quistorff, 1973). Other studies performed with **Marianne Hertz** (1943–) dealt with the BBB during electroconvulsive seizures. With repeated seizures, the barrier became increasingly permeable, and the increased permeability was linked to a marked blood pressure increase. Thus, transection of the spinal cord prevented the increase of blood pressure and of BBB permeability (Bolwig et al., 1977). Later studies showed that this was not a consequence of disrupted tight endothelial cell junction, but caused by increased vesicular transport across the endothelial cells (Westergaard et al., 1978). In this environment, **Ralf Hemmingsen** (1949–) in his early career published experimental studies in rats on CBF following alcohol withdrawal in rats (Hemmingsen et al., 1979). He later became professor of psychiatry and Vice-Chancellor of the University of Copenhagen. Other studies performed in the laboratory dealt with CBF regulation, including studies of the renin–angiotensin system as discussed below.

Marianne Hertz also made clinical studies on the BBB. This includes a remarkable discover of heterogeneity of the cerebral capillary perfusion with heterogeneous capillary transit times (Hertz & Paulson, 1980). The heterogeneity was further flow dependent with capillary recruitment at high flow levels (Hertz & Paulson, 1982). Later, Gitte Moos Knudsen and others joined the BBB

research, and collaboration was established with Cliff Patlak, Stony Brook. Heterogeneity was described in further details, and the influence of insulin on glucose distribution in the brain was investigated (Knudsen et al., 1990).

Olaf B. Paulson (1940–) had in the mid-1960s started as a young fellow in Lassen's group. He wrote his theses on rCBF in stroke and demonstrated among others that vasodilatory stimuli may have the opposite effect reducing flow in ischaemic tissue (Paulson, 1970, 1971). Paulson, specialising in neurology, was in the early 1970s appointed at the Mayo Clinic in Rochester, Minnesota, for 1 year. From 1975 and for the rest of his career, he was appointed as consultant at the Department of Neurology at Rigshospitalet. He succeeded Erik Skinhøj as chairman of the department in 1979 and became professor of neurology at the University of Copenhagen. He later established a close collaboration in the early 1970s with the psychiatrist Tom Bolwig and investigated in particular the BBB. Some studies were related to electroconvulsive therapy; see further below in this section. Other demonstrated that the BBB is very tight to water, there is no passage through slits between endothelial cells as in other organs and only diffusion across the endothelial cells takes place (Paulson et al., 1977).

Several studies in the 1980s and 1990s dealt with the regulation of the cerebral circulation both in collaboration with Lassen as described above and in collaboration with the nephrologist **Svend Strandgaard** (1939–). With Strandgaard, special emphasis was directed towards autoregulation and relation to hypertension. Autoregulation denotes that the CBF is constant within wide limits of the arterial blood pressure. The role of the renin–angiotensin system was investigated, and blocking the system shifts the autoregulatory borders to lower blood pressure values (Barry et al., 1984). Later studies proved the presence of a cerebral renin–angiotensin system independent of the systemic renin–angiotensin system. Thus, in nephrectomised rats, blocking of the renin–angiotensin system had no longer an effect on blood pressure, whereas the cerebral effect was preserved with decrease of the limits of autoregulation (Pedersen et al., 2003).

Gunhild Waldemar's studies on Alzheimer's disease and other forms of dementia with SPECT were among the first to demonstrate patterns with areas of reduced flow in Alzheimer's disease (Waldemar et al., 1994). Her interest in dementia and memory disturbances was much broader with main clinical interests, and from the mid-1990s, she established a memory and dementia clinic in the Department of Neurology at Rigshospitalet as described later in this review.

Paulson managed to get the first PET scanner to Denmark in March 1990, and the first PET scanning in Denmark was performed at Rigshospitalet. The scanner was bought second hand from Montreal, and **Albert Gjedde** who was head of the PET unit in Montreal was instrumental in securing the event. The scanner had limited resolution and was therefore predominantly used to study aspects of cerebral glucose metabolism. Studies included starvation in man, and after 3 days, one-fourth of the glucose metabolism is replaced by ketone body metabolism (Hasselbalch et al., 1994). In the coming years, new PET scanners were installed in the Department of Clinical Physiology and Nuclear Medicine at Rigshospitalet, and a strong collaboration was established with Paulson's group. Functional activation using PET of $H_2{}^{15}O$ became an important research area. **Ian Law** (1963–) joined the research group as young physician and later became consultant in the Department of Clinical Physiology and Nuclear Medicine at Rigshospitalet and professor at the University of Copenhagen. Among the results was the activation in visual association areas in response to saccadic eye movements (Law et al., 1997) including eye movements in the dark (Law et al., 1998). In 1996, these research activities provided the basis for the establishment of the Neurobiology Research Unit at the Department of Neurology at Rigshospitalet (Knudsen et al., 2013). Collaboration with the MR Department at Hvidovre Hospital was reinforced when Paulson as mentioned below took over the leadership of the department simultaneously to the establishment of the Neurobiology Research Unit at Rigshospitalet in 1996.

Gitte Moos Knudsen (1959–) joined the research group at Rigshospitalet in the 1980s and defended her thesis on the BBB permeability in 1994 (Knudsen, 1994); see also above. At the same time, as she finished her training as neurologist. In the 1990s, she studied CBF in preclinical and clinical settings with collaborators from neurology, hepatology, cardiology and infectious disorders, for example, demonstration of preserve CBF autoregulation in most patients with liver cirrhosis (Larsen et al., 1995). In 1999, she was appointed professor at the University of Copenhagen, and in 2004, she became chairman of the Neurobiology Research Unit at Rigshospitalet. Under her leadership, the Neurobiology Research Unit expanded considerably, with a whole new generation of young international research talents. The expansion was boosted by a major grant from the Lundbeck Foundation in 2005 with Knudsen as PI: The Centre for Integrated Molecular Brain Imaging (Cimbi) and by further major grants in the next decade. She established a structured data inventory and biobank, the Cimbi database and biobank (Knudsen et al., 2016), which was made freely available to other

scientists. The topics included development and use of novel radioligands for clinical brain studies, for example, imaging of the dopamine transporter and the serotonin system with SPECT and PET (Adams et al., 2005; Aznar et al., 2003; Frokjaer et al., 2008). The research became cross-disciplinary, now including not only medical doctors but also, for example, neuroscientists, engineers, physicists, biostatisticians and psychologists (Beliveau et al., 2017; Nørgaard et al., 2019). Focus has also been directed towards mode of action of antidepressants, seasonal affective disorders and the relationship between behaviour (Kalbitzer et al., 2010; Madsen et al., 2019).

Albert Gjedde (1946–) started his research in the early 1970s with Christian Crone at the Department of Physiology at the University of Copenhagen. They conducted studies of the transfer of ketone bodies across the BBB and found it increased during starvation (Gjedde & Crone, 1975). Later in the 1970s, he joined Fred Plum's group at Cornell University in New York, and the studies included investigation of the effect of chronic hyperammonaemia induced by portacaval shunt showing an increase of CBF but not of oxidative metabolism (Gjedde et al., 1978). In the late 1970s, he returned to Copenhagen to join Christian Crone's group and continued research on the BBB and of brain metabolism including neurovascular coupling. Among his achievements should be mentioned his contribution to the Gjedde–Patlak plot, also called Patlak or Patlak–Rutland plot used in pharmacokinetics tracer analysis (Gjedde, 1982).

In the mid-1980s, Gjedde's scientific interests were directed towards PET research, and he moved to Montreal to the McConnell Brain Imaging Centre at McGill University and became some years later leader of the centre. In 1994, he returned to Denmark to be chief of the new PET centre in Aarhus. Among the findings were lateralisation of phonetic and pitch discrimination in speech processing (Zatorre et al., 1992) and studies of the dopamine release in pathological gamblers (Linnet et al., 2010). In 2008, Gjedde moved to a position at the University of Copenhagen, and David Brooks (formerly Imperial College, London) took over the leadership of the PET Centre's research.

Leif Østergaard (1965–) became connected to the PET/MR centre in Aarhus after graduation from medical school and has continued his research activities in the field. As mentioned below, he took over the leadership of the Centre for Functional Integrative Neuroscience (CFIN) in 2003. He was the same year appointed as professor of experimental neuroradiology at the University of Aarhus.

A milestone was reached with the establishment of the **Centre for Functional Integrative Neuroscience (CFIN)** in 2001 thanks to a grant from the Danish National Research Foundation (see further below). Albert Gjedde was the centre's chairman until the end of 2003, whereafter Leif Østergaard took over the leadership. CFIN's research was based partly on Albert Gjedde's research on brain metabolism and dopaminergic neurotransmission using PET, for example, showing increased cerebral D2 dopamine receptors in drug-naive schizophrenic patients (Wong et al., 1986), showing link between attention deficit hyperactivity disorder (ADHD) symptoms and dopamine neurotransmission (Rosa-Neto et al., 2005), and partly on Leif Østergaard and Peter Vestergaard-Poulsen's methodological research on brain perfusion and brain networks using magnetic resonance imaging (MRI) and PET (Østergaard et al., 1996, 1998).

CFIN's research activities were gradually expanded and continued to do so in the new millennium. Several younger scientists joined the activities and became new team leaders. Thus, cognitive neuroscience was reinforced under the leadership of **Andreas Roepstorff** (1967–). Together, Leif Østergaard and Andreas Roepstorff obtained funding support for the establishment of MINDLab, an interdisciplinary research initiative that in addition to CFIN's established research also included areas such as basic physics and stochastic geometry for advanced MRI (Hougaard et al., 2014). The grants also made it possible to establish CFIN's magnetoencephalography (MEG) facility in 2010, so far, the only MEG centre in Denmark (Vuust et al., 2009). **Peter Vuust** (1961–) established studies of brain function and activation based on music as a research field at CFIN and MINDLab (Vuust et al., 2005). They showed among others that jazz music activates the dominant left hemisphere in expert jazz musicians in contrast to activation of the non-dominant right hemisphere in non-musicians (Vuust et al., 2009). Another senior collaborator is **Morten Kringelbach** (1970–). Kringelbach is also professor at Oxford University (where his Hedonia Research Group is based). Kringelbach's research at CFIN, to a large extent performed in collaboration with Vuust, was centred around music perception, cognition, emotions and interaction with motor behaviour (Kringelbach & Berridge, 2017; Matthews et al., 2019; Witek et al., 2014).

CFIN participates in close research collaborations with clinical researchers at AUH's neuro-departments, for example, in stroke, dementia, neuromodulation, psychiatry and neurointensive treatment. This research has, for example, included use of MRI to evaluate time delay in relation to thrombolysis in acute stroke treatment in collaboration with Grethe Andersen (Thomalla et al., 2018) as well as presurgical mapping of the brain's fibre pathways. Current research areas among others also include development of MRI methods for studies of the capillary perfusion heterogeneity (Jespersen &

Østergaard, 2012) and MRI studies of structural and vascular aspect in relation to Alzheimer's disease done in collaboration with David Brooks (Nielsen et al., 2020).

Jes Olesen (1941–) was a disciple of Erik Skinhøj and Niels A. Lassen. He specialised in neurology and was appointed for 1 year at New York Hospital (now Weill Cornell Medical Centre). He wrote his thesis in Copenhagen on CBF including pharmacological considerations (Olesen, 1974). Olesen became professor of neurology at the University of Copenhagen and chairman of the Department of Neurology at Glostrup Hospital in 1983. He continued his research in the field of and demonstrated cortical spreading depression as the mechanism of migraine with aura (Olesen et al., 1981). Later, he started a collaboration with Lars Edvinsson (1947–) who was working both in Lund, Sweden, and in Copenhagen. Edvinsson investigated several vasoactive substances, among these calcitonin gene-related peptide (CGRP) located in cerebral vessels and closely related to the trigeminal nerve (McCulloch et al., 1986). Later, Olesen investigated several substances that could provoke migraines. Notable was the discovery that CGRP could provoke attacks in patients suffering from migraine (Lassen et al., 2002). Subsequently, he demonstrated that CGRP also could provoke migraine in volunteers not suffering from migraine and further that treatment with CGRP blockers could prevent the migraine attack in these volunteers (Petersen et al., 2005) as it did in patients with migraine (Olesen et al., 2004). A new milestone was reached; migraine was a specific biological entity in the frame of headache. In 2021, Edvinsson and Olesen were with two other scientists (Peter Goadsby and Michael Moskowitz) awarded the Brain Prize sponsored by the Lundbeck Foundation for their transformative work on the causes and treatment of migraine. Several co-workers and younger fellows have been involved in the extensive headache research. Among these were **Rigmor Jensen** (1954–) investigating epidemiology and comorbidity in headache (Jensen & Stovner, 2008) illustrating a significant burden of headache for both patient and society.

Jens Astrup (1943–) had as young fellow started his neuroscientific career with **Niels A. Lassen**. Studies dealt with the role of potassium in the regulation of CBF, both in the healthy brain and during ischaemia (Astrup et al., 1977). Together with **Lindsay Symon** and **Bo Siesjö**, they introduced the concept of the ischaemic penumbra, referring to the surrounding of a severe ischaemic lesion where the tissue still is alive, at least for some time, but has lost its function due to partial lack of oxygen (Symon et al., 1977). These are the well-known surroundings that we nowadays aim to save by thrombolysis and endovascular therapy.

Niels Henry Secher (1946–) trained as anaesthesiologist and had a main research interest in cerebral function and muscle exercise. From 1992, he was appointed at Rigshospitalet and became professor of anaesthesiology in 2004.His research in neuroscience dealt with circulatory aspects of the cerebral function. Several studies dealt with the use of ultrasound to evaluate the cerebral circulation, for example, demonstration of flow increase in the middle cerebral artery territory during dynamic exercise, both without load and more marked during load (Jørgensen et al., 1992). Among his other research interests, we will draw attention to brain-derived neurotrophic factor (BDNF) in relation to endurance training investigated in both humans and mice. The results indicate that training induces an increased BDNF expression in the hippocampus in mice and an enhanced release of BDNF from the human brain following training (Seifert et al., 2010). In addition, we would like to mention a special exotic study in giraffes. They were anaesthetised and suspended in the upright position, and the head was moved from the upright to the drinking position. Carotid diameter and flow remained constant despite marked changes in cerebral venous pressure (Brøndum et al., 2009). Some of Secher's studies were done in collaboration with **Bjørn Quistorff** (1944–), professor in metabolic biochemistry at the University of Copenhagen. They dealt with the cerebral metabolism during exercise. During maximal exercise and in the following recovery phase, cerebral lactate is increased, and in the recovery phase, the cerebral oxygen/glucose–lactate ratio decreases (Ide et al., 2000). Further aspects of the cerebral metabolism in relation to exercise were investigated (Van Hall et al., 2009), but the basis for and mechanism of the increased non-oxidative brain uptake of glucose + lactate remained a puzzle (Rasmussen et al., 2010).

Martin Lauritzen (1952–) started his research career in the early 1980s in the environment of the research team at the Department of Neurology at Rigshospitalet. He specialised in clinical neurophysiology and became chief of the department at Glostrup Hospital in 1994 and professor in clinical physiology in 1998 as well as in translational neuroscience in 2007 at the University of Copenhagen. His early research dealt with CBF and especially with the focal flow reduction occurring in migraine attacks. He showed that the focal oligemia in migraine with aura was preceded by focal hyperaemia and that the oligemia spread like the spreading depression phenomenon of Leao (Lauritzen et al., 1983b; Olesen et al., 1981), and this formed the basis for his DMSc thesis in 1988. This led to future studies of the vascular events accompanying the depolarisation waves of spreading depression in the cerebral cortex of rodents (Lauritzen, 1987). Spreading depression was not limited to migraine but

occurred in several conditions of brain damage, such as stroke, subarachnoid haemorrhage and traumatic brain injury, and might here aggravate the brain damage (Lauritzen et al., 2011). The biological background for the spreading depression was further studied, including coupling between neuronal/synaptic activity and blood flow. Fast Ca^{++} signals may initiate the CBF response, and it was suggested that an immediate interaction between neurons and astrocytes is a basic mechanism in neurovascular coupling (Lind et al., 2013). Lauritzen later studied the regulatory mechanism of brain blood vessels and the BBB. Using mouse models, he explores the mechanisms that guide vascular cells to direct blood and hence oxygen and glucose to active neurons (Cai et al., 2018). Specific parts of the small blood vessels control the traffic of substances between blood and brain, and signalling molecules in the blood contribute to vascular network properties. More recent studies deal with transport across the BBB of small hydrophilic substances that can cross the BBB when encapsulated in small hydrophilic nanoparticles, a mechanism of potential major therapeutic implication (Kucharz et al., 2021). In mouse and human studies, Lauritzen's research further explored the effect of brain ageing on cognition with emphasis on the relation between brain structure, blood flow, cognitive ability, health and lifestyle factors (Henriksen et al., 2017).

Ole Henriksen (1944–2006) who had his background in clinical physiology became the chief of the first magnetic resonance (MR) scanner and first MR department in Denmark in 1983. A new dimension was reached in Danish neuroscience, and the hospital administration decided that the scanner, which was donated by the Spies Foundation, should form the basis of a new MR research department, also taking care of some clinical duties. Henriksen reinforced in Denmark the new MR research field. He established international collaboration and attracted researchers from abroad. Among these were **Freddy Ståhlberg** from Lund, who later became the leading figure in MR research in Lund. Among his Danish disciples were **Henrik BW Larsson** (1957–) and **Carsten Thomsen** (1955–), both of whom had main impact on the field in the coming years. Among the achievements of Ole Henriksen's group, they were the first to show reduced water diffusion in cerebral ischaemia and multiple sclerosis (MS) (Larsson et al., 1992; Thomsen et al., 1987). They also quantified the passage of gadolinium into the brain tissue and thereby the BBB damage (Larsson et al., 1990) and used water as reference in MR spectroscopy (Christiansen et al., 1993). These methodological developments are now standards in clinical and research MR.

Ole Henriksen unfortunately became unexpected acutely severely disabled in 1995, only 10 years after he had established the department. **Olaf Paulson** was asked by the Copenhagen Hospital Corporation to take over the leadership of the department simultaneously to his appointment as professor of neurology at Rigshospitalet. Functional brain imaging became among others an important field of research, for example, visual stimulation during sleep resulted in 'deactivation' in visual areas (Born et al., 2002). International collaboration was strengthened, and in 2001, a grant for the first 3-T MR scanner in Denmark was obtained by the Spies Foundation. Combined PET-MR research was established in collaboration with Rigshospitalet (Grady et al., 2013), Paulson further reinforced a broad collaboration in the Copenhagen area, and already in 2003, he approached the university with the aim of establishing 7-T MR facilities in the Copenhagen area and wrote later the applications resulting in funding in 2009 and 2010 based on the Copenhagen collaboration. Later in 2010, Hvidovre Hospital's management ended the Copenhagen collaboration by autocratically appointing Hartwig Siebner (1965–) from Germany as Olaf Paulson's successor.

In psychiatry, neuroimaging studies addressing psychiatric diseases developed to a main research area with many contributors. **Raben Rosenberg** (1946–) and **Tom Bolwig** studied rCBF by SPECT of inhaled ^{133}Xe in depressed patient before and between the single treatment with electroconvulsive therapy. No regional disturbances were observed, but global CBF was elevated before treatment and returned gradually to normal levels during treatment (Rosenberg et al., 1988). **Ralf Hemmingsen** addressed schizophrenia. Drug-naïve patients studied with SPECT had impaired activation and performance (Rubin et al., 1991). Later studies with MRI in first episode teenagers revealed frontal white matter changes and enlarged ventricles (Pagsberg et al., 2007). **Poul Videbech** (1956–) has initiated neuroimaging research of affective disorder with PET in collaboration with Centre of Functionally Integrative Neuroscience, Aarhus, for example, the observation of unchanged activation pattern in major depression despite slower performance (Videbech et al., 2004). Some years later, **Birte Glenthøj** (1951–) headed a Lundbeck Foundation research unit in Glostrup for non-treated schizophrenic patients. This formed the target for neuroimaging research with PET and MR, including actions of antipsychotic drugs, for example, attenuation of activation during reward anticipation (Nielsen et al., 2012), as well as low binding potential of dopamine D2/3 receptors related to a better treatment response in drug-naive schizophrenics (Wulff et al., 2015). Extensive research on mood disorder including depression and reward systems has been done by Lars Kessing (1959–) and co-workers in Copenhagen, including a postdoc (Kamilla Miskowiak). They studied treatment of depression with erythropoietin

and observed that improved recall was related to increased activation in the dorsolateral prefrontal cortex (Miskowiak et al., 2015). They also investigated the neural response fMRI to electroconvulsive therapy (Miskowiak et al., 2018). Brain imaging study in depression has also been performed by **Tom Bolwig** and **Martin Balslev Jørgensen** (1955–) and co-workers investigating the influence of electroconvulsive therapy on the brain by MR. They observed increased volume in hippocampus and amygdala and reduced volume in other regions. The biochemical profile remained unchanged (Jorgensen et al., 2016).

Extensive translational research took place at the Center for Psychiatric Research at Aarhus University Hospital headed by **Raben Rosenberg** and **Poul Videbech** aiming at integrating basic and clinical psychiatric research. A cross-disciplinary group included expertise on animal behaviour, molecular biology, genetics, pharmacology, stereology and neuroimaging in close collaboration with clinical departments (Ahdidan et al., 2011; Dalby et al., 2010; Videbech et al., 2004; Wegener et al., 2000, 2003).

4.2 | Trends in the evolution of psychiatry

This section of the chapter deals with scientific achievement in psychiatry not related to the clinical physiological area described above. The Central Danish Psychiatric Register has been a wealth to many researchers and has resulted in a large number of studies elucidating important epidemiological aspects and also causal factors of many psychiatric disorders taking advantage of the registers being of excellent quality and populations based. **Povl Munk-Jørgensen** (1946–) headed the register when situated at Aarhus University Hospital. The register was moved to Faculty of Social Science, and the research responsibility was handled by **Preben Bo Mortensen** (1959–) (Munk-Jørgensen & Mortensen, 1997). The register continues to be a valuable tool in national health planning and in epidemiological research. It is almost complete for major psychiatric disorders (Mors et al., 2011).

4.2.1 | Psychopharmacology

A brief description of the ***Laboratory of Neuropsychiatry*** seems relevant here. As described above in Chapter 2, section 'Neuropathology', it was established in 1898 as the University's Psychiatric Laboratory at Kommunehospitalet and moved to Rigshospitalet in 1934. In 1968, it was reorganised and continued as the Psychochemistry Institute under Ole Rafaelsen's leadership. The Laboratory of Neuropsychiatry is now a research laboratory at the Department of Psychiatry at Rigshospitalet and part of the University of Copenhagen. It is headed by a steering group consisting of Anders Fink-Jensen, Gitta Wörtwein and Morgane Thomsen.

After Rafaelsen's appointment in the Department of Psychiatry at Rigshospitalet in 1965, psychiatric research was reinforced in the Psychiatric Laboratory/Psychochemistry Institute. Thus, **Erling Mellerup** (1939–) joined the laboratory in 1966, and **Per Plenge** (1942–) and **Ole Steen Jørgensen** (1944–2018) joined a few years later. They all three were basic scientists and later became associate professors at the University of Copenhagen. Together with Rafaelsen and other scientists, they reinforced the basic science in biological psychiatry, resulting in many publications, for example, on lithium's interaction with magnesium distribution in rats (Mellerup et al., 1973), on basic aspects of cerebral membrane proteins (Jørgensen, 1995), on variations blood platelet serotonin transporters related to genetic variation in bipolar disorders patients (Mellerup et al., 2001) and on antidepressants binding to the serotonin transporter (Plenge et al., 2007).

Independently, the Danish research in psychopharmacology has had international impact with important contributions from the University Clinics in Aarhus and Copenhagen; see review by Vestergaard (2011). Lithium research (described earlier) was continued as an important activity both in Aarhus (**Per Vestergaard,** 1941–) and Copenhagen (**Lars Kessing**) with evaluation of side effects (Vestergaard et al., 1980) and risk of suicide (Smith et al., 2009). Significant contributions by **Ib Munkvad** (1921–1998) and **Axel Randrup** at Sankt Hans Hospital in Roskilde were important for the development of the dopamine hypothesis for schizophrenia (Randrup & Munkvad, 1966, 1967). **Jes Gerlach** (1938–) also at Sankt Hans Hospital addressed the pathophysiology of tardive dyskinesias, a side effect of treatment with antipsychotics (Gerlach et al., 1975). Pharmacogenetic and kinetics studies were topics for several groups, especially professors **Lars Gram** (1938–) and **Kim Brøsen** (1954–) in Odense (Brøsen et al., 1993).

Anders Fink-Jensen (1959–) joined the group of Morten Møller and Jens D. Mikkelsen just after he graduated from medical school. They studied the circuits underlying the circadian rhythm (see Chapter 4). He soon got connected with NOVO Nordisk where he was appointed from 1987 to 1997 and became 'Research leader'. Here he worked with uptake inhibitors for the neurotransmitters GABA and dopamine as well as on other drugs acting on specific receptors (Bymaster et al., 1998; Fink-Jensen et al., 1992). He returned to the

postgraduate medical specialisation, became professor in 'biological psychiatry' in 2012 and joined the Laboratory of Neuropsychiatry, of which the main focus is to educate biological researchers. In that laboratory, the main focus is the biological mechanisms underlying psychiatric disorders. One important focus in the laboratory is related to drug and alcohol addiction. He and his colleagues have demonstrated that GLP-1 receptors are expressed in brain areas involved with reward and addiction, such as the ventral tegmental area and nucleus accumbens in rodents, humans and non-human primates. The GLP-1 system has therefore attracted interest as a potential target for treating addictions. GLP-1 receptor agonists have shown promise in reducing alcohol intake in rodents (Brunchmann et al., 2019) and monkeys (Thomsen, Holst, et al., 2019) and also in relation to food and water intake (Tang-Christensen et al., 1996).

4.2.2 | Genetics in psychiatry

Fini Schulsinger (1923–2012) became professor of psychiatry in Copenhagen in 1971 after serving as chief physician at Kommunehospitalet in Copenhagen from 1960 to 1971. Schulsinger's major contributions to psychiatry are several studies elucidating the gene–environment interaction in a variety of psychiatric illnesses, most famously in schizophrenia and mood disorders. Several of the studies were carried out in collaboration with Seymour S. Kety and colleagues from the United States. The investigations included studies of adopted children revealing a clear genetic disposition for schizophrenia (Rosenthal et al., 1971) and even more markedly for mood disorders (Wender et al., 1986).

Aksel Bertelsen (1936–2019) became leader (1987–2006) of WHO's reference centre at the Psychiatric Hospital in Aarhus/Risskov. The research included worldwide studies of schizophrenia showing that the incidence is similar in different cultures, but the outcome milder in developing countries (Jablensky et al., 1992). Schulsinger's and Bertelsen's work has placed Danish psychiatry importantly on the world map.

Schulsinger and Bertelsen took great advantage of the populations-based register for which Denmark is internationally famous. Their work has been succeeded by several of their followers in Denmark and abroad. Molecular genetic studies have since even augmented the reputation of Danish genetic research including the iPsych study supported by the Lundbeck Foundation and headed by **Ole Mors** (1952–), Aarhus, **Merete Nordentoft** (1955–), Copenhagen, and **Thomas Werge** (1962–), Sankt Hans Hospital. The overall purpose of this study is new insight in the classical gene–environment interaction in psychiatric disorders, and findings include description of novel genetic variants in schizophrenia (Steinberg et al., 2011).

4.2.3 | Psychopathology

Despite many new research methods in psychiatry, the description and classification of mental disorders are still most often based on psychopathology. Thorough psychopathological analysis remains mandatory for delineation of nosological entities. Danish psychiatry has a long tradition for this important aspect of clinical activity and research. **Josef Parnas** (1950–), Copenhagen, has contributed significantly to the psychopathology of schizophrenia applying methods from philosophy, especially phenomenology (Sass & Parnas, 2003); see also Chapter 4.

Another approach to psychopathology is psychometrics, that is, construction and validation of rating scales. The research of **Per Bech** (1942–2018) has had international impact generating rating scales for depression, mania and quality of life (Bech et al., 1979).

4.2.4 | Social psychiatry

Merete Nordentoft (1955–), Copenhagen, has contributed significantly, especially in suicidal behaviour, psychopathology and early intervention in psychosis (Nordentoft et al., 1993). She was PI for many large randomised clinical trials, evaluating the effect of psychosocial intervention, of which the Danish OPUS trial (specialised assertive intervention in first episode psychosis in younger patients) is the most well known. OPUS in not an acronym, but taken from the music world to symbolise harmony. The OPUS trial has resulted in a large number of publications, including the start of the project (Jorgensen et al., 2000), the 10 years' evaluation (Secher et al., 2015) and a more recent evaluation (Posselt et al., 2021).

4.3 | Trends in the evolution of neurological specialities

Neuroscience in the field of clinical physiology and brain imaging was as described above a dominating field of research. However, other fields in clinical Danish neuroscience also achieved significant results and reached new milestones.

4.3.1 | Clinical neurophysiology

A main contribution to diagnosis of neuromuscular diseases was established in Danish neurology by **Fritz Buchthal** and his group in the 1940s and 1950s, which introduced clinical neurophysiology. His contribution to Danish neuroscience at large is described in Chapter 4. Following Buchthal's retirement in 1977, **Werner Trojaborg** (1923–2015) took over the leadership of the Department of Clinical Neurophysiology at Rigshospitalet, and after him, in 1991 **Christian Krarup** (1947–). Independently, **Martin Lauritzen** took over the leadership of the other Department of Clinical Neurophysiology at Glostrup Hospital in 1998. Martin Lauritzen's research is described previously in the present chapter. Trojaborg had his training with Buchthal. After his retirement in Denmark, he was appointed at the Department of Neurology at Columbia Presbyterian Hospital, New York (1991–1997). Trojaborg's research dealt with all aspects of neuro-electrophysiology, and especially with the peripheral nervous system (Hansen et al., 1989). Soon after his graduation, Christian Krarup joined Buchthal's group in Copenhagen. Part of his training as research fellow took place at National Hospital for Nervous Diseases, London. In 1982, he joined as visiting scientist Fritz Buchthal, who after his retirement in Copenhagen had moved to NIH, Bethesda, USA. In1984, he was appointed as director of clinical neurophysiology at Brigham and Women's Hospital, Boston, Massachusetts. In 1990, he returned to the Department of Clinical Neurophysiology at Rigshospitalet in Copenhagen and was nominated professor a few years later. Krarup's (Hansen et al., 1989) research has been translational with both experimental and clinical studies and focuses on especially peripheral nerves and on nerve repair (Fugleholm et al., 1994; Krarup-Hansen et al., 2007).

One of the first clinical neurophysiologist in Aarhus was **Palle Juul-Jensen** (1929–1998). As mentioned above, his scientific interest was epilepsy, and he had main skills in administration of benefit for neuroscience and the University of Aarhus (Juul-Jensen & Brown, 1966; Juul-Jensen & Foldspang, 1983). **Viggo Kamp Nielsen** (1936–2012) followed Juul-Jensen as chief of clinical neurophysiology in Aarhus. His research dealt to a large extent with peripheral nerves, for example, with peripheral nerve function in renal failure and with carpal tunnel syndrome among slaughterhouse workers (Frost et al., 1998; Nielsen, 1974).

Anders Fuglsang-Frederiksen (1946–) was for many years chief of clinical neurophysiology in Copenhagen at Gentofte Hospital and moved to Aarhus around the millennium after Viggo Kamp Nielsen's retirement. He started his scientific career in Buchthal's laboratory, and throughout the years, electrical muscular activity, muscular physiology and muscular diseases have been his main field of research (Fuglsang-Frederiksen, 2006; Fuglsang-Frederiksen & Scheel, 1978). Other parts of his research have dealt with peripheral neuropathies, pain and aspects of epilepsy including interaction between epilepsy and cardiac function (Jeppesen et al., 2019; Qerama et al., 2010).

4.3.2 | Neurodegenerative disorders

Memory disorders and dementia became a clinical and research focus area in the mid-1990s. **Gunhild Waldemar** (1957–) was a pioneer and established the Danish Dementia Research Centre at Rigshospitalet in Copenhagen. The centre has played a major role in Danish dementia care, research and education. Waldemar had her background in clinical neurology in the environment of the Department of Neurology at Rigshospitalet. Her early research dealt with CBF with special focus on dementia; see earlier in this chapter. She was appointed as professor of neurology in 2006. **Steen Gregers Hasselbalch** (1958–) has completed his thesis on PET studies of the glucose metabolism using the tracer ^{18}F-deoxyglucose at the Neurobiology Research Group. He was a leading clinical specialist from the early development of the memory clinic and was affiliated full time and appointed clinical professor from 2013 with focus on early diagnostic biomarkers. The clinic has a large research activity with extensive international collaboration. The scientific results include quality of life investigation in early Alzheimer's disease and its relation to anosognosia and depression (Vogel et al., 2006), studies showing widespread reductions in the 5-HT2A serotonergic receptor binding in amnestic mild cognitive impairment patients, which correlated to the cognitive deficit (Hasselbalch et al., 2008), and studies showing a positive effect of exercise in Alzheimer patients on neuropsychiatric and depressive symptoms, but not on cognitive tests (Hoffmann et al., 2016).

Movement disorders and Parkinson's disease became focus areas already in the 1960s at Kommunehospitalet. Later, these focus areas moved to Hvidovre Hospital and later again to Bispebjerg Hospital. **Henning Pakkenberg** (1920–2007) took the early initiative with interest in both clinical and research aspects. Part of the studies were translational in experimental animals (Fog et al., 1970) and others clinical observations (Burns et al., 1985). Throughout the years, neuronal cell counting in normal and diseased brains was a main area of research (Korbo et al., 1990; Pelvig et al., 2008). Part of these studies were done with sophisticated stereological

methods by his daughter **Bente Pakkenberg** (1949–2023) in collaboration with **Hans Jørgen G. Gundersen** (1943–2021) (Pakkenberg et al., 1991); see further in Chapter 4.

In the western part of Denmark, research and clinical activities were directed towards Parkinson's disease from around 1990 by **Karen Østergaard** (1952–) starting with studies of dopaminergic neurons in slice cultures. Subsequently, investigations dealt with cell transplantation in animal models of Parkinson's disease and studies of neurotrophic factors (West et al., 1996). Later towards the new millennium, she and the neurologist **Erik Dupont** (1936–) together with the neurosurgeon **Niels Sunde** (1951–) introduced deep brain stimulation (DBS) in Denmark (Østergaard et al., 2002), at first for essential tremor and Parkinson tremor targeting the ventral-intermediate nucleus of thalamus, a few years later targeting the subthalamic nucleus to treat not only tremor but also 'off' periods with bradykinesia and rigidity in Parkinson's disease. In the 2000s, dystonias, especially primary generalised dystonia and focal dystonia as cervical dystonia, were included among neurological diseases treated with DBS; in case of dystonia, the target was the internal part of globus pallidus. Through the years, research and treatment by DBS has resulted in a considerable number of publications and several PhD studies led by the Aarhus group.

At the Department of Genetics at the University of Copenhagen, **Sven Asger Sørensen** (1936–2021) had throughout the years a main interest in genetics of neurodegenerative diseases, and especially in Huntington's disease. His research included mutations in genetics in relation to age of onset in Huntington's disease (Nørremølle et al., 1993) and frontotemporal dementia (Skibinski et al., 2005) and natural history of von Recklinghausen neurofibromatosis showing increased cancer risk in severe cases in female (Sørensen et al., 1986).

4.3.3 | MS

In the early 1950s, **Torben Fog** (1912–1987) at Kommunehospitalet in Copenhagen became an international leading figure in MS research. Fog's early work was on spinal cord pathology and encephalomyelitis in MS (Fog, 1950). Later, he and co-workers demonstrated strong genetic factors in MS by the association between histocompatibility haplotype HLA antigens and MS (Jersild et al., 1973). Fog already in 1980 pioneered the use of interferon in the treatment of MS more than a decade before its approval. These early results were negative as consequences of the combination of interferon type and category of MS; see description in a well-known textbook (Rudick et al., 1996).

In 1956, the Danish Multiple Sclerosis Registry was established (Hyllested, 1961), unique in its character with recording of almost all (>90%) Danish MS cases and now embedded in the Danish Multiple Sclerosis Centre (DMSC), leading to excellent research and international collaboration in the field of epidemiology of multiple sclerosis (Koch-Henriksen, 1999; Magyari et al., 2016).

At Rigshospitalet in the 1990s, it became possible to establish the DMSC, headed by **Per Soelberg Sørensen** (1944–), now one of the largest MS centres in Europe. Basic, translational and clinical research were reinforced. International collaboration expanded and new clinical trials were initiated (Sorensen et al., 2003, 2009, 2014). Under his leadership, a new generation of enthusiastic MS researchers grew up in DMSC, including Finn Sellebjerg (1964–) with immunology as main interest and Jette Frederiksen (1959–) with optic neuritis as her specialty.

4.3.4 | Stroke

Frederiksberg Hospital in Copenhagen had special attention directed towards stroke under the leadership of Torvald Dalsgaard-Nielsen (1896–1975). The Department of Neurology had a large number of hospital beds, sufficient to create what nowadays would be called a stroke unit for the whole population of Frederiksberg municipality, 120,000 inhabitants—the first Danish stroke unit. The stroke patients had extensive clinical work-up with daily clinical neurological examination for the first days, and most of the patients who died had an autopsy performed. Still the clinical differential diagnosis between haemorrhage, thrombosis and embolism as compared to autopsy was, as the authors expressed, amazingly low (Dalsgaard-Nielsen, 1956). In the following years, John Riishede (1918–1988), Bent de Fine Olivarius (1922–2005) and Jørgen Marquardsen (1920–1989) all wrote their DMSc theses on stroke (de Fine Olivarius, 1964; Marquardsen, 1969; Riishede, 1957). Riishede did his research in at the Department of Neurosurgery in Aarhus, and Olivarius and Marquardsen in Dalsgaard-Nielsen's department. All three dealt with the clinical cause of stroke related to clinical symptoms, pathology, angiography and other aspects. The neuropathologist Erna Christensen (Chapter 2) participated in the supervision of Olivarius thesis. Riishede later became chief of neurosurgery at Rigshospitalet and professor of neurosurgery, Olivarius chief of neurology in Aarhus and professor of neurology at Aarhus University, and Marquardsen chief of neurology in Aalborg. Marquardsen continued his research on stoke, for example, on prophylactic treatment for reversible cerebral ischaemic attack with acetylsalicylic acid (Sorensen et al., 1983).

New approaches to stroke diagnoses, treatment and research can to a vast extent be ascribed to **Gudrun Boysen** (1939–). She started her research with a vascular surgeon **H. C. Engell** (1920–2010). She continued her activities throughout the coming decades at Rigshospitalet and later as professor at Hvidovre and Bispebjerg Hospital. Her early field of research dealt with CBF during operation for carotid artery stenosis and occlusion (Boysen et al., 1971). She demonstrated that the vasomotor activity is preserved during hypocapnia, but not during hypercapnia, a finding of main interest for planning the surgical intervention. Her later field of research activities dealt with atrial fibrillation as a risk factor for stroke (Petersen et al., 1989) and with thrombolysis in strokes, both in experimental models (Andersen et al., 1999) and in the clinical setting, the latter with vast international collaboration (Hacke et al., 1995, 1999). Olaf Paulson also investigated the cerebral circulation in stroke; see above in the present chapter. In the 1990s before the modern acute stroke treatment took off, **Tom Skyhøj Olsen** (1945-) investigated several aspects of stroke, for example, CBF disturbances (Olsen et al., 1983), and he drew attention to stroke units in order to secure relevant rehabilitation (Jorgensen et al., 1995).

Independently, **Grethe Andersen** (1956–) in Aarhus started activities dealing with stroke treatment and research in the late 1990s (Andersen et al., 1995). Her activities continued in the new millennium, and she contributed to introducing intravascular therapy for acute stroke (Simonsen et al., 2018). At present, thrombolysis takes place in many departments of neurology in Denmark, but intravascular therapy is concentrated in Aarhus for the western part of Denmark and at Rigshospitalet in Copenhagen for the eastern part. Andersen further investigated the potential effect of remote ischemic preconditioning (on/off ischaemia of the arm) on acute stroke (Hougaard et al., 2014).

4.3.5 | Headache and pain

The earliest interest in Denmark for headache research should be ascribed to **Torvald Dalsgaard-Nielsen**, mentioned above under stroke, at Frederiksberg Hospital in Copenhagen. His migraine research dealt predominantly with treatment of migraine as well as its epidemiology (Dalsgaard-Nielsen, 1970). He wrote a book on migraine addressing laymen as well as professionals (Dalsgaard-Nielsen, 1972). See also review on the history of Danish headache research by **Peer Tfelt-Hansen** (1944–) (Tfelt-Hansen, 2001). Tfelt-Hansen himself was also a migraine researcher dealing among other aspects with the effect and side effects of ergotamine treatment (Tfelt-Hansen & Krabbe, 1981).

A remarkable contribution to headache research was carried out through several decades by Jes Olesen, leading to the Brain Prize as described earlier in this chapter.

Interest in pain research and treatment in Danish neurology emerged from the headache activities in the 1980s described earlier in this chapter and independently from **Troels Staehelin Jensen's** (1947–) research activities in Aarhus in the 1980s. He got part of his scientific training in neurobiology at the Mayo Clinic, Rochester, Minnesota, in 1983 and became in 1994 leader of the Danish Pain Research Centre affiliated with the Department of Neurology in Aarhus and later professor of neurology at Aarhus University. Many of his early studies were experimental, for example, stereotactic injection of morphine in experimental animals (Jensen & Yaksh, 1986) but included also clinical studies, for example, on painful phantom limb sensations (Jensen et al., 1983). He became a leading figure in Danish pain research and treatment throughout the following decades and has been joined by **Flemming Winther Bach** (1955–) in Aarhus and by **Søren Sindrup** (1956-) in Odense. These groups have especially studied the consequences of injury and diseases affecting the peripheral and central nervous system leading to neuroplastic changes and pain. They examined how specific disorders such as nerve injuries including limb amputations, neuropathies, spinal cord lesions and stroke may alter processing of somatosensory information and eventually cause pain (Finnerup et al., 2005; Jensen et al., 2001). The Aarhus group, now led by Nanna Brix Finnerup (1965–), pointed out specific treatments for these types of neuropathic pain (Finnerup et al., 2010). In Aalborg, **Lars Arendt Nielsen** (1958–) investigated pain, for example, his group showed that tonic pain reduces the excitability of motor cortical and spinal neurons (Le Pera et al., 2001). See also Chapter 4.

4.3.6 | Neuromuscular diseases

In Aarhus, **Johannes Jakobsen** (1945–) reinforced the interest for peripheral nerve diseases with interest in diabetic neuropathy in the late 1970s (Jakobsen et al., 1981). Jacobsen had his training in Aarhus and at Rigshospitalet in Copenhagen. In 1974–1979, he was visiting scientist at the Peripheral Nerve Laboratory, Mayo Clinic, Rochester, Minnesota, and in 1989–1990 at the Neuroimaging Labs Research Centre for Mallinckrodt Institute of Radiology in St Louis. From 1992, he was professor of neurology at Aarhus University. Later, his research was expanded to other aspects of neurological manifestation in diabetes and other neuromuscular diseases (Andersen et al., 2004).

In the eastern part of Denmark, the treatment of patients with muscular diseases mostly took place at

Rigshospitalet. In the 1980s, much focus was directed towards myasthenia gravis and severe cases of Guillain–Barré syndrome, both centralised to Rigshospitalet (Somnier et al., 1991). In the 1990s, a dedicated unit for muscular diseases headed by **John Vissing** (1960–) was established in the Department of Neurology. Vissing started his postgraduate training in 1986 as research fellow in basic science for 3 years at the University of Copenhagen including one and a half years stay at the University of Texas, Dallas. He was appointed as consultant at the Department of Neurology at Rigshospitalet in 1995 and as professor in neurology at the University of Copenhagen in 2001. The early research was experimental, for example, demonstrating that static muscle contraction reflexly increases sympathetic nerve activity to the adrenal gland (Vissing et al., 1991). Later extensive research was basic and applied clinical, for example, paternal mitochondrial DNA being responsible for myopathy (Schwartz & Vissing, 2002) and glucose utilisation in McArdle's disease (Haller & Vissing, 2002). The unit has since expanded and is now a main player in Danish neuroscience.

4.3.7 | Neurosurgery

In the mid-1980s, a new generation of leaders took over both in Aarhus, Odense and Copenhagen. In Copenhagen, **Flemming Gjerris** (1936–) took over the leadership of the Department of Neurosurgery at Rigshospitalet in 1985. His fields of research were directed towards brain tumour in children (Gjerris & Klinken, 1978) and especially towards intracranial pressure, for example, conductance to CSF outflow as a predictor of outcome (Børgesen & Gjerris, 1982) and a historical review on the topic (Gjerris & Snorrason, 1992). **Marianne Juhler** (1955–) was appointed as professor in 2008 at the Department of Neurosurgery at Rigshospitalet and did her early research in experimental studies in rats, for example, increased BBB permeability to small molecules preceding histological changes in experimental allergic encephalomyelitis (Juhler et al., 1984) and later focused on clinical aspect, especially on intracranial pressure, for example, on the pathoanatomical basis for normal pressure hydrocephalus (Bech et al., 1997).

In Odense, **Per Kærgaard Bjerre** (1945–1918) has throughout the years had interest in the pituitary gland's function and in pituitary adenoma (Nielsen et al., 2007).

In Arhus, **Jens Astrup** became the new leader and professor in neurosurgery in 1987. In 2004, he moved to be chairman and professor in the Department of Neurosurgery at Glostrup Hospital. His research has been described above under neuroscience in the area of clinical physiology. Other parts of his research were directly related to neurosurgical topics, for example, optic glioma (Astrup, 2003). **Jens Christian Sørensen** (1960–) became professor in Aarhus in 2006. His research branches over several fields including neurodegenerative diseases (Bjarkam & Sørensen, 2004) and device development (Bjarkam et al., 2004).

Studies on DBS have been discussed above under neurodegenerative diseases.

4.3.8 | Neuropathology

In the preceding chapter (the section on psychopharmacology), it was mentioned that the Psychiatric Laboratory became the Psychochemistry Institute in 1968 under Ole Jørgen Rafaelsen's leadership.

As mentioned in the previous chapter neuropathology was in Denmark established in the Psychiatric Laboratory in 1898. In 1968, the neuropathological department was reorganised as the new University Department of Neuropathology established under the leadership of **Leif Klinken** (1924–2012). In 1996, the university Department of Neuropathology was moved to Rigshospitalet's clinical Department of Pathology and was renamed the *Laboratory of Neuropathology* (within the University's Institute of Molecular Pathology with three laboratories, one of which was the Laboratory of Neuropathology). Klinken's research was to a large extent related to neurosurgical aspects, for example, long-term survival of astrocytoma in children (Gjerris & Klinken, 1978) and leptomeningeal changes related to CSF outflow resistance in normal-pressure hydrocephalus (Bech et al., 1997). Other studies were experimental and dealt with, for example, brain flow and oxygen consumption during alcohol withdrawal (Hemmingsen et al., 1979). **Nils Henrik Diemer** (1944–2023) became the leader of this *Laboratory of Neuropathology*. He and his research group had a broad spectrum of activities. Among the activities were a major focus on pathological changes of oligodendroglia and astroglia, for example, revealing hyperammonemia caused a reversible transformation of glial nuclei (Diemer & Laursen, 1977). Other studies investigated the effects of ischaemia, for example, revealing a selective vulnerability of the hippocampal CA-1 pyramidal cells but sparing the hippocampal interneurons (Fryd Johansen et al., 1983). He further studied the toxic effect of glutamate released during ischaemia and introduced with co-workers 'microdialysis' (described in Chapter 4).

4.3.9 | Paediatric neurology

The 1950s can be considered the decade where attention also was directed towards research in child neurology. **Preben Plum** (1906–2002) was professor of paediatrics from the early 1940s and had a broad spectrum of paediatric research activities including neuroscience with special interest in cerebral palsy (Plum, 1956, 1958).

Child neurology research was further developed by **Johannes Melchior** (1923–1995). He had part of his education in paediatrics and neurology at Harvard Medical School in Boston and became professor of paediatrics in the early 1970s at the University of Copenhagen and a few years later also chairman of the Department of Paediatrics at Rigshospitalet. He had a main role together with Bengt Hagberg from Sweden in founding the Nordic Neuropaediatric Society, formed at Rigshospitalet in 1963. Melchior had a broad interest in neuropediatric research (Hagberg & Uldall, 2021). Among the fields were studies of cerebral palsy, partly done in collaboration with the neuropathologist Erna Christensen (Christensen & Melchior, 1967) and of rare diseases of early childhood including the description of the Dyggve–Melchior–Clausen syndrome, a genetic condition characterised by abnormal skeletal development, microcephaly and intellectual disability (Dyggve et al., 1977).

Peter Uldall (1949–) was consultant at the Danish Epilepsy Hospital Filadelfia from 1992, Filadelfia is a hospital specialised in epilepsy, established in 1897 and situated 100 km west of Copenhagen. It plays a main role in epilepsy care and research and participates in the national program for presurgical evaluation of epilepsy patients. From 1997, Uldall was consultant at the Department of Neuropaediatrics at Rigshospitalet from 1997 and became professor of neuropaediatrics at the University of Copenhagen. His neuropediatric research had special focus on childhood epilepsy and cerebral palsy. The research includes studies on treatment and diagnosis of epilepsy (de Knegt et al., 2020; Uldall et al., 1995, 2006). Risk of cerebral palsy and childhood epilepsy related to infections before or during pregnancy (Wu et al., 2013) and on cerebral palsy as discussed below in the section on neonates.

The *Danish Cerebral Palsy Register* was founded in 1967. Data had already been collected from 1925, partly by Erik Hansen (1927–2008). The register covered for many years only the eastern part of Denmark, but has since 2001 covered all of Denmark (Uldall et al., 2001).

Hans C. Lou (1939–) was chief of the Neuropediatric Department at the John F. Kennedy Institute located in the suburbs of Copenhagen. The institute was established in 1967 as a national counselling and research centre for genetics, visual impairment and mental retardation. It is now part of Rigshospitalet. Lou had a broad research activity related to child neurology. It included studies of CBF and brain damage in neonates as described further below. Several studies dealt with different genetic diseases, a key focus at the Kennedy Institute, for example, with phenylketonuria (Okano et al., 1991) and with Fabry's disease (Lou & Reske-Nielsen, 1971). Other studies in the more recent years dealt with mental status and brain imaging in adults (Kjaer et al., 2002).

At the Aarhus University Hospital, **John Østergaard** (1953–) was consultant and associate professor. His research included studies on genetic diseases in childhood, for example, Angelman syndrome (Trillingsgaard & Østergaard, 2004) on febrile convulsions including studies using the Danish register system (Vestergaard et al., 2008) and on intracranial aneurysm in childhood (Ostergaard & Voldby, 1983).

Neuro-neonatology

A pioneer in Danish neonatology was **Bent Julius Friis-Hansen** (1920–2002). He had part of his training at Harvard University as a research fellow in surgery, also involved in investigation in children. In 1964, a Department of Neonatology was established at Rigshospitalet with Friis-Hansen as chief. In 1970, he was appointed as professor at the University of Copenhagen. Assisted ventilation and improved treatment of premature children were introduced (Greisen, 2010). The rapidly evolving neonatal intensive care allowing survival of ever smaller babies led to an increased risk of brain injury and handicapped children. This became a prime concern for Friis-Hansen, and he started a series of investigations of the long-term effect of the improved treatment. This led to further improvement of therapy with a decline in the incidence of cerebral palsy and other forms of brain damage in the coming decades (Larsen, Rackauskaite, et al., 2020; Topp et al., 2001).

Together with Niels A. Lassen (see earlier in the chapter) and younger fellows, Friis-Hansen measured CBF in the newborns. They applied intravenous (i.v.) injection of the inert gas ^{133}Xe. The investigation included autoregulation of CBF and on increased risk of cerebral haemorrhage related to hypertensive peaks (Lou et al., 1979; Wimberley et al., 1982). Other aspects of Friis-Hansen's neuroneonatology deal with other aspect of the cerebral circulation, for example, metabolic aspects (Pryds et al., 1988).

Following Friis-Hansen's retirement, **Gorm Greisen** (1951–) became chief of the Department of Neonatology in 1991 and in 1998 professor of paediatrics at the University of Copenhagen. Greisen's early studies had, for example, shown that CBF is low in preterm infants and even lower in those treated with mechanical ventilation (Greisen, 1986). He continued research on CBF in the preterm brain demonstrating, for example, that blood

flow is extremely low in the cerebral white matter of preterm human neonates (Børch & Greisen, 1998). He further addressed the cerebral blood flow autoregulation and CO_2 reactivity in the newborn; see review (Greisen, 2005). Greisen also demonstrates a short-lasting decrease in cerebral EEG activity and fall in blood pressure in neonates after the surfactant instillation for pulmonary dysfunction (Hellström-Westas et al., 1992). Near-infrared spectroscopy was applied in many studies but never got a broader clinical application, see review (da Costa et al., 2015).

4.3.10 | Other fields of clinical neuroscience

The autonomic nervous system controls a number of important organ functions. The activity of the sympathetic nervous system was until the early 1970s measured by registering variables in effector organs (pulse, blood pressure, vasoconstriction, pupil size, etc.). From the latter half of the 1970s, the circulating concentration of the sympathetic neurotransmitter noradrenaline could be measured in plasma using a reliable double-isotope derivative technique as an expression of sympathetic spill-over (Christensen, 1979). Several Danish researchers pioneered the study of autonomic activity in, for example, muscle work (Christensen & Galbo, 1983), diabetes (Christensen, 1982), surgical stress (Hilsted et al., 1983) and liver diseases (Henriksen et al., 1985). Selective organ catheterisations showed that neurotransmitter spill-over was most often uniformly increased in the various organs and tissues, but in some cases, there was a preferential increase in sympathetic tone in individual organs (Christensen et al., 1984; Henriksen et al., 1992).

The sympathetic nervous system has a major influence on CBF regulation. Thus, activation resets the autoregulation of CBF to higher pressure levels. This effect interacts with the lowering of the autoregulatory limits following inhibition of the cerebral renin–angiotensin system. This interaction was studied by Gunhild Waldemar, who showed that stimulation of the sympathetic system in rats treated with angiotensinogen-converting enzyme inhibitors resets the upper limit of autoregulation to higher values (Waldemar et al., 1989). Further, following sympathetic cervical denervation, angiotensinogen-converting enzyme inhibitors retained its lowering effect on the lower and upper limits of CBF autoregulation (Waldemar, 1990).

Sleep disorders became the main research area for **Poul Jennum** (1956–) who from the late 1990s established a centre for sleep disturbances at the Department of Clinical Neurophysiology at Glostrup Hospital, now part of Rigshospitalet. A strong research environment was created dealing with many aspects of sleep, including sleep apnoea, narcolepsy, sleep classification and sleep disturbances related to neurological diseases (Jennum & Borgesen, 1989; Jennum & Riha, 2009).

The poliomyelitis epidemic in Denmark, 1952–1953, described earlier in the present chapter, had also a main impact on *neurorehabilitation*. The need for rehabilitation was evident, and a rehabilitation hospital was established north of Copenhagen. When the need for rehabilitation after poliomyelitis diminished in the coming years, the hospital continued as a rehabilitation centre for patients with spinal cord lesion, mostly traumatic, and became part of Rigshospitalet, now as the Clinic for Spinal Cord Lesion (Biering-Sørensen & Gregersen, 2013). As leader of the clinic during the last 35 years, Professor **Fin Biering-Sørensen** (1948–) reinforced the clinical and research activities. The studies include epidemiological studies on survival (Hartkopp et al., 1997) and studies on the effect of training by electrical stimulation of the muscles (Mohr et al., 1997) and in collaboration with the pain research group in Aarhus studies on pain sensation in patients with incomplete spinal cord lesion (Finnerup et al., 2007).

4.4 | The evolution of clinical psychology

Neuropsychology got an important role in Danish neurology and psychiatry in the second half of the 20th century and is now represented in all neurology departments and in several psychiatry departments. In the same time frame, neuropsychology and biological psychology received increased attention at the Institute of Psychology at the University of Copenhagen (there were two different psychological institutes, which merged in 1999). This is further described in the subsequent section on cognitive neuroscience in chapter 4 on basic and preclinical science.

Forerunners in psychiatric psychology were **Anna Elisabeth 'Lise' Østergaard** (1924–1996) and **Alice Theilgaard** (1926–2017). Lise Østergaard's thesis dealt with thought disorders in schizophrenics (Østergaard, 1962), and part of her research was about psychology and obesity in children. She was head of psychology at the Department of Psychiatry at Rigshospitalet in Copenhagen (1958) and became the first professor of clinical psychology when the Institute of Clinical Psychology was established at the University of Copenhagen in 1963. Alice Theilgaard succeeded Lise Østergaard as head of psychology at the Department of Psychiatry at Rigshospitalet (1964). She was appointed adjunct professor at the University of Copenhagen in 1990. She had a broad research activity with a biological approach, for example, X/Y chromosomal abnormalities, particularly Klinefelter's

syndrome (Theilgaard, 1984). She also wrote a book, *Shakespeare as Prompter: The Amending Imagination and the Therapeutic Process*, together with Marry Cox exploring the field between narratology, art and psychotherapy (Cox & Theilgaard, 1994).

Rolf Willanger (1927–1995) was the first psychologist in a neurological department, appointed in 1959 at Rigshospitalet and Gentofte Hospital. He was appointed at the University of Copenhagen in 1967, and in 1972, he was nominated to a new professorship in neuropsychology at the Laboratory of Psychology. His main research achievement done in collaboration with professor in neurology. **Paul Thygesen** (1914–1999) was a comprehensive description including psychological test of Second World War concentration camp survivors (Thygesen himself had been prisoner in a German concentration camp during the war) (Thygesen et al., 1970). It was emphasised that their condition (the KZ syndrome) could be a kind of brain damage.

In the Department of Neurology at Rigshospitalet, **Peter Bruhn** (1941–) and **Anders Gade** (1946–) introduced a more norm-based approach to Danish neuropsychology, stressing the importance of normative studies to account for the effects of age and demographic factors in clinical evaluations and use of well-matched control groups in clinical studies. During the 1980s, neuropsychology became an integrated part in the evaluation of many patients with neurological diseases (Vogel et al., 2004; Waldemar et al., 1994). Anders Gade published a main book in Danish titled *Brain Processes: Cognition and Neuroscience* dealing with both international and Danish sciences (Gade, 1997).

At the Institute of Psychology at the university, **Claus Bundesen** (1948–), **Axel Larsen** (1944–) and other cognitive psychologists had developed influential models of visual attention, and beginning in the 1990s, the brain bases of visual cognition were explored with neuroimaging (Larsen et al., 2005). These aspects are further described in Section 5 of this article dealing with basic/preclinical science.

From around the turn of the millennium, several neuropsychological PhD projects of various psychiatric conditions have typically been paired with neuroimaging studies of the same patients.

5 | CHAPTER 4: THE EVOLUTION OF BASIC/PRECLINICAL NEUROSCIENCE IN THE 20TH AND BEGINNING OF 21ST CENTURY

The development of basic/preclinical neuroscience has been strongly linked to the universities and the curriculum of medical studies. Already in 1842, it was stated that there shall be examinations in anatomy (and anatomical dissection), physiology and pharmacology in the curriculum at Copenhagen University. However, it is only by the new curricula from 1873, 1902 and 1912 that anatomy, biochemistry and physiology stood out as separate subjects and thus motivated separate departments and professor positions. Even with the development of buildings, infrastructure and resources, the evolution of *science* was slow, and when it progressed, it did not include *neuroscience* until well into the 20th century. At Aarhus University, medical education started in 1933, at Odense University (now the University of Southern Denmark) by 1966, and at Aalborg University by 2010. It is difficult to organise the development of neuroscience according to anatomy, physiology and biochemistry—partly because physiological and biochemical questions often involve anatomical/histological techniques. In the 21st century, the development of new institutes/departments with specific topics (such as neuroanatomy and neurophysiology) was actually reversed. Reorganisations of the departmental structure at faculty level led to fewer departments covering larger fields—often with one 'unit' covering the whole field of neurobiology. A new development—first and foremost seen at Aarhus University—is the creation of 'networks' securing close contacts between research units at different faculties and preclinical and clinical groups into a NeuroCampus Aarhus (https://neurocampus.au.dk), which is a research cluster covering neuroscience and cognition at Aarhus University and Aarhus University Hospital that works within the neuroscience field.

Finally, a few words on the Danish Society for Neuroscience (DSfN). The society was established in 1984 upon the initiative of Christian Crone and Hans Hultborn. The founding members were a group of younger neuroscientists, Elisabeth Bock, Tom Bolwig, Albert Gjedde, Hans Hultborn, Povl Krogsgaard-Larsen, Olaf B. Paulson, Arne Schousboe and Jens Zimmer, all of whom have contributed significantly to Danish neuroscience as discussed elsewhere in this article. The society soon established a forum for scientific discussions and interaction including a well-attended annual 2-day meeting. Although the DSfN is mentioned here, it covers both basic and clinical neurosciences as is obvious from the founding members (including the clinical scientists Tom Bolwig and Olaf Paulson).

In the following description, we will follow the disciplines of anatomy, physiology, biochemistry and cognitive neuroscience. However, within this framework, we will partly follow the *timeline* and also try to keep together *groups of collaborating scientists* (also when this will include the 'next generation') and sometimes the

places (institutes/universities) where the developments were interconnected.

5.1 | Neuroanatomy

5.1.1 | Establishment of neuroanatomy in Aarhus—and subsequently in Odense

Lárus Einarson (1902–1969) was born in Reykjavik where he also got his medical degree in 1928. He had developed an interest in neuroanatomy during his studies and therefore moved to Copenhagen after his graduation. He studied histological staining techniques at the Anatomical Institute at the University of Copenhagen with Professor Frederik Carl Christian Hansen (1870–1934) for 1 year. Subsequently, he went to Munich and the United States (Woods Hole) to continue these studies and described a specific Nissl staining with gallocyin-chromalum in a highly cited publication (Einarson, 1932). After returning to Copenhagen, Einarson became assistant at the Laboratory of Pathology and subsequently at the Laboratory of Psychiatry at Bispebjerg Hospital. In 1936, he was appointed professor in Anatomy at the University of Aarhus. This university was inaugurated in 1933, and with the new medical education, it was his responsibility to create the new Institute of Anatomy. His scientific work was focused on the Nissl substance (ribosomal RNA) and the chromatin in the nuclei. He developed a staining technique that could quantify the nucleic acid turnover, which allowed to study the turnover during activity versus rest, and during pathological circumstances, for example, multiple sclerosis, stress, anoxia and poliomyelitis (Einarson & Krogh, 1955). Einarson was affiliated with the Institute of Brain Pathology at the State Mental Hospital at Aarhus (at Risskov) with access to its large brain collection.

When Lárus Einarson retired in 1967 (though he continued to work at the Institute), his position was taken over by **Theodor W Blackstad** (1925–2003) from the famous 'Oslo School of Neuroanatomy' founded by Alf Brodal and Jan B Jansen in 1930. Blackstad got his medical degree in Oslo in 1952. Already as a student, he studied a year in Paris at the Laboratoire Charcot, Hôpital La Salpêtrière. Subsequently, Blackstad visited Dr Walle Nauta (in Zürich), from whom he obtained information and protocols of a new silver impregnation method to map the connections between central neurons. He applied Nauta's new silver impregnation method to map the connection within the hippocampus—and between hippocampus and other brain structures, for example, (Blackstad, 1956). In 1956–1957, he studied histochemistry and electron microscopy in Chicago—and soon thereafter he defended his DMSc thesis in 1958. Subsequently, he used systematic combinations of immunohistochemistry and EM studies to reveal connectivity in hippocampus and other brain structures. He also used a modified Golgi preparation for electron microscopy. He became a pioneer in quantitative neuroanatomy with computer-based three-dimensional (3D) reconstructions. All this was of great importance—not least for the progress of physiological experiments on the hippocampus in Oslo. He was employed as assistant and associate professor in Oslo until 1967 and then as professor in Anatomy at Aarhus University in the period 1967–1977. His stay at the young Department of Anatomy was of greatest importance for the development of its scientific direction and strength (Blackstad et al., 1970; Geneser-Jensen & Blackstad, 1971). In 1977, he returned to Oslo to a professorship there.

Gorm Danscher (1938–) graduated as veterinarian in 1967. He wanted a career in science—and his dream had been 'brain research.' He succeeded to become assistant professor in Blackstad's Institute of Anatomy in Aarhus in 1967. A guest scientist from Oslo, Professor Fin-Mogens Haug, trained Danscher in his field, 'zinc in CNS', and in particular in hippocampus. Zinc (Zn) is essential for hundreds of enzymes and indispensable for DNA and RNA reproduction, and not least a peculiar pool of zinc is located in synaptic vesicles in many populations of neurons in the brain and spinal cord (Pérez-Clausell & Danscher, 1985). The field soon was broadened to cover many kinds of 'heavy metals' such as gold, silver, mercury, lead and selenium, with discussions on their possible biological effects. His methodological work on improving the sulphide silver method suitable for both light and electron microscopy had a strong impact (Danscher, 1981). Danscher's special interest in metallic gold was inspired by the claim that placing small pieces of gold in acupuncture points relieved pain and reduced swelling of rheumatic joints. Danscher demonstrated that implanted gold pieces indeed release gold ions. In the peripheral tissue, it was taken up in neighbouring macrophages and mast cells—these cells are mainly responsible for the oedema/swelling that is so characteristic of rheumatic joints. In the brain, the gold was taken up by neighbouring astrocytes and neurons (Danscher, 2002). Danscher was professor at the Institute of Anatomy in Aarhus from 1988 until his retirement in 2008 (and then professor emeritus). He was the chairman of the Institute of Anatomy 1997–2008.

Jens Zimmer and Bente Finsen—starting in Aarhus, moving to Odense to establish neuroanatomy/neuroimmunology at the University of Southern Denmark

Jens Zimmer (1947–) started to study medicine at Aarhus University in 1966. Two years later, during his

studies, he started as a teacher and researcher. He focused on lesion-induced reorganisation of central nervous connections and on the connections to transplanted foetal brain tissue (Haug et al., 1971; Zimmer, 1973) at the Anatomy Institute. He received his MD in 1975, and in1976, he received his MDSc degree. Afterwards, he went to Geoffrey Raisman at the University College in London for a year to study 'similar' questions at electron microscopic level. He then returned to Aarhus, but in 1991, he moved to Odense with his PhD student/colleague Bente Finsen (see below). New scientific topics deal with the interaction between brain and immune system, neuro-glial interaction (Finsen et al., 1991), the importance of microglial cells for acute and chronic neuropathology (Jørgensen et al., 1993) and the cellular and molecular mechanisms of remyelination.

Bente Finsen (1961–) studied medicine at Aarhus University, where she got her MD degree in 1988. She then joined Jens Zimmer at the Department of Anatomy and moved with Jens Zimmer to Odense in 1991 but defended her thesis in Aarhus in 1995 (Finsen, 1995). In Odense, they build up a neurobiology group (now the Neurobiology Unit in the Department of Molecular Medicine; University of Southern Denmark). This was done by recruiting advanced scientists from abroad (Trevor Owens) and by recruiting researchers and students locally. From 1998 to 1999, Bente Finsen was a visiting scientist at McGill University. Her present research focus includes (i) microglial immunity in Alzheimer's disease, (ii) regulation of remyelination in multiple sclerosis and (iii) microglial neuroprotection in stroke. Her interest in inflammatory cytokines is clearly reflected by some high-impact reviews (Heneka et al., 2015; Lambertsen et al., 2012).

Trevor Owens (1952–) came from McGill University (in 2004) with a background in *immunology*, developing into *neuro*immunology (Babcock et al., 2006). Since 2010, Trevor Owens has been the leader of the entire Neurobiology Unit. Research in the Neurobiology Unit is now concentrated on injuries and diseases of the CNS such as MS (Hjæresen et al., 2021; Martin et al., 2018), Alzheimer's disease, Parkinson's disease (Bogetofte et al., 2019), stroke (Lambertsen et al., 2012; Yli-Karjanmaa et al., 2019) and spinal cord injury. The studies involve the interactions between the immune system and glial cells of the nervous system, both those that lead to pathology as well as with regulatory and protective outcomes. One of the goals is to understand how innate and adaptive immune cells and mediators contribute to neurological disease. Largely, the field could be described as 'molecular neuroscience', but histological methods certainly remain as a tool. There is a close association between Odense University Hospital (OUH) and Neurobiology Research at the Department of Molecular Medicine, University of Southern Denmark. That collaboration strongly involves the early recruitment of Kate Lykke Lambertsen (e.g., Lambertsen et al., 2012, 2019).

In Copenhagen, the similar fields were covered by the professors **Nils Henrik Diemer** (1944–2023) and **Flemming Fryd Johansen** (1952–) and others at the Institute of Neuropathology (later a *Laboratory* within the Institute of Molecular Pathology). This resulted in several co-publications between Jens Zimmer and other members of the Neurobiology unit in Odense (see further in Chapter 3). From 2008, Nils Henrik Diemer actually moved to Odense and joined the Neurobiology Unit there.

5.1.2 | Neuroanatomy finally established in Copenhagen

There was a slow start for neuroanatomy—and histochemistry—at Copenhagen University. Following Frederik C. C Hansen's comprehensive body of work on haematoxylin staining at the turn of the century, there was only relatively modest activity within histochemistry-related research at the Institute of Medical Anatomy in Copenhagen for almost the next 50 years. This situation changed radically when, having got his MD degree in 1957, **Helge Andersen** (1929–1995) was recruited to work as assistant professor at the Institute of Anatomy in 1959. In the following year, he set up and subsequently was leading the Laboratory of Cyto- and Histochemistry. When the Institute of Anatomy was divided into three Institutes (A, B and C), Helge Andersen became associate professor and chairman at Medical Anatomical Institute **A** from 1965 until his retirement in 1983.

In the summer of 1968, after the MD exam, **Kjeld Møllgård** (1942–) was hired to work as a research assistant at the institute (following 4 years of student employment as a demonstrator and anatomical instructor). Kjeld Møllgård had previously expressed an interest in working with human brain development, and Helge Andersen had agreed to teach him histochemistry and embryology, and at this time, he needed someone working on the development on the human adenohypophysis. Helge Andersen had innumerable histochemical methods running in the lab. He also had the basic material available, for example, hundreds of paraffin blocks from extremely well-fixed human foetuses. The histochemical work produced by/at the Laboratory of Cyto- and Histochemistry in the mid-1980s reflected developments in the research field and included not only classical histochemistry but also fluorescence histochemistry, immunohistochemistry

and quantitative histochemistry using 'up-to-date' EM methods, including immunogold labelling.

Over the past 40 years, Professor Kjeld Møllgård's areas of research interest include developmental neurobiology (Møllgård & Saunders, 1986; Saunders et al., 2014), brain-barrier systems, embryology, stem cells and organogenesis. One of Kjeld Møllgård's recruits, **Torben Moos** (1963–), became professor at Aalborg University, and he is now leading a neurobiology research unit at the Department of Health Science and Technology (at the Faculty of Medicine). They focus on the cell biology of the BBB and the neurovascular unit, targeted therapy at the BBB, and more recently, nanoparticle transport at the BBB in order to enable drug transport across the BBB (Kucharz et al., 2021; Thomsen, Linemann, et al., 2019).

Morten Møller (1942–) also joined Helge Andersen's laboratory at about the same time as Kjeld Møllgaard. They have several co-publications from that time (mainly on the development of the subcommissural organ and the pineal gland of the human foetus). After some years, Morten Møller and younger recruits as Jens Damsgaard Mikkelsen (see more below) and Anders Hay-Schmidt focused on the innervation of the mammalian pineal gland, reviewed in Møller and Baeres (2002). This work was often performed in close collaboration with Jan Fahrenkrug (Møller et al., 1985) and Jens Hannibal (1953–), both from Dept. for Clinical Biochemistry at Bispebjerg's Hospital (see below). This line of research was expanded to a mapping of the photo-neuroendocrine system consisting of the retina, the suprachiasmatic nucleus of hypothalamus and the pineal gland by use of neuronal in vivo tracing techniques and immunohistochemistry. In a combined effort involving neuroanatomical and molecular biological techniques, they have subsequently been studying the development and function of the circadian system of the mammalian brain. In recent years, the group—with several new members—has continued to deepen the work on circadian rhythms. They have shown that homeobox gene-encoded transcription factors are essential in both development and mature function of the circadian neuroendocrine system (Rohde et al., 2014). There has been a focus on the pinealocyte, the principal melatonin-producing cell type of the pineal gland. They have shown that the circadian system extends from the hypothalamus into other parts of the brain, including the cerebral cortex and the cerebellum, both of which receive a circadian input from the hypothalamus (Rath et al., 2013, 2014). They have recently published results on a novel conditional knockout mouse, showing that disruption of the cortical circadian clock affects monoamine signalling inducing symptoms of depression (Bering et al., 2018); thus, they have used a basic scientific approach to shed light on the aetiology of a major psychiatric disorder.

Jens Damsgaard Mikkelsen (1960–) joined Morten Møllers laboratory as a medical student in 1982 and worked on the pathway from retina to the pineal gland (Mikkelsen & Møller, 1990). After obtaining his MD in 1986, he applied recently introduced neuroanatomical tracing techniques, such as the *Phaseolus vulgaris* leucoagglutinin (PHA-L) method (Gerfin & Sawchenko, 1985), that allowed him to trace neuronal connections between tiny areas and nuclei within the rat brain (Mikkelsen, 1990). Using this technology, later combined with immunocytochemistry and in situ hybridisation, the group identified several new connections between the internal clock, the suprachiasmatic nucleus and other regions in the brain. He received his DMSc in 1993 (the neural basis of circadian rhythms). In the early 1990s, new researchers with medical backgrounds joined Mikkelsen's team such as Philip Just Larsen, Niels Vrang and Mads Tang-Christensen. Jens Damsgaard Mikkelsen's team became interested in describing connections, neurotransmitters and receptors in other autonomic and neuroendocrine systems such as stress pathways (Larsen & Mikkelsen, 1995) and feeding behaviour and metabolic control. All group members continued their work as independent researchers either at the University or in the industry. From 1995, Mikkelsen took over research management roles in various industries. He returned to Copenhagen University as a clinical professor at the Neurobiology Research Unit, Rigshospitalet, in 2009, and in 2021, he became professor in translational neuropharmacology at the Institute of Neuroscience and study director for the new Master of Science Education in Neuroscience. His research was now translational and directed towards neuroreceptors (Santini et al., 2013; Thomsen & Mikkelsen, 2012).

Both **Jan Fahrenkrug** (1947–2021) and **Jens Hannibal** (1953–) had their main relation to the Department of Clinical Biochemistry at Bispebjerg Hospital (part of the Copenhagen University Hospital). Both of them were particularly focused on the actions of the 'circadian clock' onto the endocrine system, and therefore, they are described here in relation to Morten Møller and JD Mikkelsen with whom they had much collaboration. **Fahrenkrug** started his medical career at the Medical Endocrinology at Bispebjerg Hospital in 1973. He was mainly interested in diseases related to hormonal dysfunction, in particular diabetes, and for the hormones in the intestinal tract that participate in regulating the production of insulin. Many of those peptides such as vasoactive intestinal polypeptide (VIP) and pituitary adenylate cyclase activating polypeptide (PACAP) are actually found in neurons, and thus, his interest in the nervous system started (Fahrenkrug, 1979). The focus was to map the occurrence and function of neuropeptides and neuropeptide receptors and clarify their patho-biochemical role in

disease (Christiansen et al., 2016). As described above, he was collaborating with Morten Møller and Jens D. Mikkelsen on the neuronal control of the circadian rhythm, an interest that has followed him until present time (Holland et al., 2018). When Jan Fahrenkrug retired from his professor position in early 2021, he was succeeded by his colleague **Jens Hannibal** (1953–) who has shared the interest in the circadian rhythm, and not least the retinal aspects. The common interest extends to a general interest in identifying specific neuropeptides in specific cell types, their receptors/transmitters, and as far as possible their function. Their latest co-publication in this field is actually from 2021 (Georg et al., 2021).

5.1.3 | Stereology: Collaboration between Aarhus and Copenhagen

Stereology is the 3D interpretation of two-dimensional cross sections of materials or tissues. It provides practical techniques for extracting quantitative information about a 3D material from measurements made on two-dimensional planar sections of the material. In the modern era of stereology (from the 1970 onwards), the Danish scientist **Hans Jørgen G Gundersen** (1943–2021; MD from Aarhus university by 1970) made important contributions to sensitive, accurate and precise quantitative methods (Gundersen, Bagger, et al., 1988; Gundersen, Bendtsen, et al., 1988). Historically, quantitative methods generally made assumptions about the organ, tissue or structure of interest. The statistical and mathematical principles used in modern stereology guarantee that no assumptions—or bias—in principle are introduced in the analysis. These new stereological methods spread rapidly to the rest of the world and are today considered the 'gold standard' in quantitative anatomy and histology. The Stereology Research Laboratory was established in 1987 at Aarhus University, and Gundersen was elected professor in Stereology. **Mark J West** (1945–) collaborated closely with Gundersen. They made major contributions to the development of the new generation of basic stereological methods (Gundersen, Bendtsen, et al., 1988). He worked at the Stereological Research Laboratory at the Institute for Experimental Clinical Research; later as professor at the Anatomical Institute; and finally at the Neurobiology Unit at Department of Biomedicine. At the last place, he focused on the Alzheimer's disease and recently worked together with Morten Skovgaard Jensen on the capillary network on aged transgenic mice mimicking the Alzheimer disease (Nikolajsen et al., 2015).

In collaboration with Henning Pakkenberg and **Bente Pakkenberg** (1949–2023), daughter of Henning Pakkenberg (see also Chapter 3), the new stereology methods were quickly applied to the human brain. Over time, several surprising results have originated from stereological publications and include, for example, that the total number of neurons in the neocortex is 16% (4 billion) higher in men than in women (Pakkenberg & Gundersen, 1997). However, the IQ is not correlated to the number of neocortical neurons (Songthawornpong et al., 2020). Further, chronic alcoholic and Alzheimer patients do not lose neocortical neurons in spite of the heavy drinking in the alcoholics and severe cognitive deficits in Alzheimer patients (Badsberg Jensen & Pakkenberg, 1993; Regeur et al., 1994).

5.2 | Neurophysiology

Johannes Lindhard (1870–1947) had a pivotal position in the establishment of science-based research in the academic studies of gymnastics (the 'theory of gymnastics' at the University of Copenhagen). He was professor in the theory of gymnastics from 1917. He started his scientific career rather late as he worked as a physician for some years before participating, as physician, in a Danish expedition to Greenland during 1906–1908. Before this expedition, he met with August Krogh to discuss how he could do some physiologic measurements of the crew in relation to extreme temperatures and the major shifts in daylight durations between summer and winter. As he returned, he intended to spend the rest of his life in experimental physiology. Much of this was done in collaboration with August Krogh, and most of the work focused on respiration, blood flow and metabolism during exercise in humans. In one early publication with August Krogh on the regulation of respiration and circulation during the *initiation* of hard muscular work, they described the abrupt rise in pulmonary ventilation and heart rate, long before any metabolic need. They concluded that this sudden increase was due to *an* 'irradiation of impulses from the motor cortex' otherwise used to activate the muscles (Krogh & Lindhard, 1913). Another part of the work that could be included in the field of neuroscience was directly related to the recording of the electromyogram during voluntary muscle contraction (Henriques & Lindhard, 1920, 1923). The neuro-muscular transmission, with electrophysiological recording of the action potentials from the end-plate region and the muscle cell, was performed together with **Fritz Buchthal** (see below). The collaboration between Lindhard and Buchthal included a project in which they measured the shortening of different parts of the sarcomere during contraction of single muscle fibres (isolated from the frog) (Buchthal et al., 1936).

The 'electro-physiology' in neurosciences in Denmark was introduced, rather coincidentally, by a German of Jewish origin, **Fritz Buchthal** (1907–2003)

(Figure 3), who was forced to leave Germany in 1933 and was invited to work together with Johannes Lindhard.

In 1925, Fritz Buchthal started medical school at the University in Freiburg im Breisgau. A year later, he left for California in protest of the rising of the 'Deutsche Nationalismus'. In 1927, Buchthal passed the entrance examination to Stanford where he studied anatomy, genetics, biology and physiology. Under the tutelage of Nobel laureate J. J. R. Macleod, he became interested in muscle physiology. In 1928, he returned to Germany to finish medical school at Friedreich Wilhelms Universität in Berlin. During the last year of the medical studies and in the following year, he worked at the Institute of Physiology under Professor Wilhelm Trendelenburg and Professor Erich Schütz, with whom he completed his medical thesis on the contractions and action potentials of the frog heart. He then joined the 'Kaiser Wilhelm Institut für Biologie', headed by Professor Tibor P. Peterfi, and developed microelectrodes to record single muscle fibre potentials. This work was written in 1932 but published in 1934 (Buchthal & Péterfi, 1934). But this was also the end of his stay in Germany. One morning in April 1933, he was suddenly refused to enter his office and was asked to leave the Institute. Ten days later, he was invited by Johannes Lindhard at the laboratory for the theory of gymnastics at the University of Copenhagen to join his laboratory. Besides the basic work with Lindhard, Fritz Buchthal also started a clinical EMG-collaboration, first with Svend Clemmensen at Kommunehospitalet (in 1938) for diagnosing neurological patients. This continued in 1939 with the start of the Clinical Neurophysiology Laboratory at Rigshospitalet. During the Second World War, when problems suddenly accelerated in Denmark in October 1943, Buchthal fled to the neutral Sweden. There he worked at the Institute of Physiology at the University of Lund where many young Swedish physiologists benefited from his teaching.

He returned to Copenhagen in May 1945. At the recommendation of Danish scientists, including August Krogh and Niels Bohr, and economically supported by the Michaelsen Foundation, the Carlsberg Foundation, the Rockefeller Foundation and the Danish state, the Institute of Neurophysiology was built in the late 1940s and inaugurated in 1952 with Buchthal as director. He was later appointed professor of neurophysiology in 1955.

5.2.1 | Fritz Buchthal's recruitment of basic neurophysiologist to the Institute of Neurophysiology

Over the years, the Institute and the Department of Clinical Neurophysiology continued to expand the field of neurophysiology, and Buchthal attracted many bright physicians, engineers and scientists—not only in his own field but also in 'neurophysiology' a large. Among those we would like to mention are Ove Sten-Knudsen (1919–2007), later professor of biophysics; Henning Schmalbruch (1938–), the specialist in morphological techniques, including electron microscopy; Annelise Rosenfalck (1922–2004), with a degree in electronic engineering from the Danish Technical University; and Poul Rosenfalck (1924–1976, a physicist), Arne Mosfeldt Laursen (1928–2004), later appointed professor in behavioural physiology (see further below); Ivan Divac (1932–1999) (also behavioural physiology; see further below in the Section on Cognitive neuroscience); and Margaret Lennox (1913–2001) who was focusing on cortical physiology and epilepsy. We will focus on the scientific discoveries emerging from this Institute in the following sections.

Fritz Buchthal's own greatest contributions were in the clinical arena where he and his group characterised and quantified the motor unit and their electrical activity, both in normal subjects of different ages and patients with various neuromuscular diseases, using novel recording devices such as concentric, bipolar and multilead electrodes (Buchthal et al., 1954, 1957). He also advanced the study of nerve conduction by developing the near-nerve stimulating and recording technique so as to record evoked potentials not only from large myelinated fibres but also from smaller myelinated A-delta fibres (Buchthal & Rosenfalck, 1971a, 1971b). With these and other neurophysiological and histopathological methods, the effects of disease states such as poliomyelitis, anterior horn cell disorders and various peripheral nerve and muscle diseases were revealed. The morphological and electrophysiological studies of several neuropathies were instrumental in our understanding of the differentiation of axonal and demyelinating peripheral neuropathies based on the degree of slowing of peripheral nerve conduction (Behse et al., 1972). Not to be ignored were the Buchthal group's early contributions to use serum levels of anticonvulsants for correlation of the incidence of paroxysmal abnormalities in the electroencephalogram in the management of patients with epilepsy (Buchthal et al., 1960).

Annelise Rosenfalck (1922–2004) received her degree in electronic engineering from the Danish Technical University in 1947. Her master's project was carried out at the Institute of Neurophysiology, under Buchthal's guidance. During the next 3 years, she worked with DISA Electronics developing electrophysiological equipment, while in her free time she still worked with Buchthal at the Institute. In 1950–1951, Annelise Rosenfalck studied at MIT, Cambridge, and at Yale University, USA, and after her return to Copenhagen in 1951, she worked at

FIGURE 3 Fritz Buchthal around 1977.

the Institute of Neurophysiology as associate professor. During these years, Annelise Rosenfalck, in collaboration with Fritz Buchthal, made important contributions to the fields of nerve and muscle physiology, and in particular, the development of near-nerve electrodes and the reduction of electronic noise for the recording of sensory nerve action potentials in humans (Buchthal & Rosenfalck, 1971b; Guld et al., 1970). Their combined efforts revolutionised the study of patients with neuropathy. Together with her husband Dr Sci. Poul Rosenfalck, she built a team of fundamental significance for the development of the Institute.

Henning Schmahlbruch's independent contributions were very strong. He described the specific fibre types in human muscles (Schmalbruch & Kamieniecka, 1974) reviewed the motor unit of mammalian muscles (together with Buchthal; Buchthal & Schmalbruch, 1980) and the motoneuron death following axotomy at different developmental stages (Schmalbruch, 1984). At the end of his career, he became increasingly interested in possible treatments for delaying motoneuronal death in progressive neuropathies. He finally published a textbook on 'skeletal muscle' (Schmalbruch, 1985).

Arne Mosfeldt Laursen (1928–2004) was born in Denmark, but his university studies were made in Michigan, USA, where he graduated before becoming an MD at the University of Copenhagen in 1955. In 1958, Arne Mosfeldt Laursen was employed at the Institute of Neurophysiology, and 2 years later, he became associate professor in physiology at the Psychology Laboratory. In 1963, Mosfeldt Laursen got his DMSc thesis on corpus striatum (Laursen, 1963). Afterwards, he returned to the Institute of Neurophysiology, and in 1969, he was appointed professor of behavioural physiology. His main research topic was motor behaviour following lesions or stimulation of motor centres—an important conclusion was that many previous opinions on the contribution of specific motor centres actually could be ascribed to destruction/activation of *neighbouring* structures rather than those primarily aimed for. These experiments were performed in monkeys. During this period, **Poul Dyhre-Poulsen** (1942–2008) joined the group, and he later developed collaboration with a group of anatomists interested in biomechanics to study the locomotor movements and the underlying spinal excitability together with **Fin Bojsen-Møller** (1933–) and **Erik Simonsen** (1955–). In this collaboration on the human gait, Dyhre-Poulsen was responsible for the electrophysiological testing of, for example, the spinal excitability during stepping (Simonsen & Dyhre-Poulsen, 1999). In 1978, Mosfeldt Laursen made an important scientific 'U-turn' by spending time in Oslo with Professor Per Andersen and learning, and adopting, his technique of using brain slices for investigations of cellular mechanisms in various brain centres under in vitro conditions. Mosfeldt Laursen was, directly or indirectly, recruiting several young students to join these projects back in Copenhagen: **Jørn Hounsgaard** (see below), **Henrik Jahnsen** (1951–), **Jens Rekling** (see below) and **Jens Midtgaard** (1960–)—all of whom also spent years at the best laboratories worldwide to broaden the perspectives and pave the way for individual research projects. All of them became associate professors at the neurophysiology group in Copenhagen, and Jørn Hounsgaard was later promoted to full professorship in neurophysiology (see further below). Altogether, this was a very important impetus for the introduction of modern basic neurophysiology in Copenhagen—and Denmark.

5.2.2 | Neurophysiology in Copenhagen after Buchthal's retirement

Fritz Buchthal retired from his position in 1977. He continued his research after his formal retirement, from a laboratory space in a new section of the hospital where he studied human nerve action potentials evoked by tactile stimuli. From 1982 to 1984, he directed an EMG laboratory at NIH in Washington, DC. He then settled in Santa Barbara in California with his wife. Until the age of 90, he continued to work as a consultant at Children's Hospital in San Francisco.

When Fritz Buchthal retired from his professor position in 1977, the faculty decided to open the position, but with the specification that it should be closely linked to *basic science*. The leadership of *clinical* neurophysiology was taken care of by Werner Trojaborg (until 1994), and subsequently by Christian Krarup and Martin Lauritzen. In 1980, **Hans Hultborn** was appointed professor of neurophysiology, and the entire Institute of Neurophysiology had just moved to the Panum Institute, the new building for basic sciences at the Medical Faculty in Copenhagen.

Hans Hultborn (1943–) was coming from Gothenburg University where he had been working in Anders Lundberg's renowned group. By electrophysiological methods, the 'Gothenburg group' had studied how descending pathways controlled motoneurons and spinal reflex pathways in the control of movement (Baldissera et al., 1981). Hultborn's focus was on the pathway and interneurons mediating reciprocal inhibition (Hultborn, 1972). Since these experiments were done in anaesthetised animals, the interpretation of the function during voluntary movement in humans was 'tentative'. In order to overcome these limitations, Hultborn started a collaboration with Emmanuel Pierrot-

Deseilligny's group at the Salpêtrière Hospital, Paris. They were identifying the same systems (spinal reflex pathways) in humans and studied how reflex transmission from afferent feedback was controlled during voluntary movement (Hultborn et al., 1987). One young collaborator, **Jens Bo Nielsen**, joining Hultborn's laboratory in the early 1980s, soon became a leader of this translational research (from anaesthetised animals to humans performing voluntary movements), now also including electrical and magnetic activation of the corticospinal tract (see further below).

Another field in focus in Hultborn's laboratory in the beginning of the 1980s and onwards was the analysis of a persistent inward current in motoneurons, which strongly controlled the strength of synaptic excitation of the motoneurons, thus controlling the gain of the activation of the muscles—and thus of movements. In this major project, Hultborn was joined by **Jørn Hounsgaard** who had great experience with cellular neuronal properties from his work in in vitro preparations, including his post.doc period with Charles Nicholson, New York University (see further below). Another young collaborator, **Ole Kiehn** joined the group at this time, and he participated in the projects on persistent inward currents—both with Hultborn and with Hounsgaard (Hounsgaard et al., 1988). Ole Kiehn also contributed to another project from the early 1980s—the finding and analysis of the sensory afferent control of 'fictive locomotion' (Conway et al., 1987) that can be evoked in the decerebrate unanaesthetised animals. The sensory afferent feedback is of great importance during real locomotion (studied elsewhere), and Hultborn has returned to several aspects of this field in preparations with 'fictive locomotion'. In order to establish the in vivo mouse techniques (also allowing experiments in transgenic preparations), the group recruited a postdoc in 2007 (Claire Meehan). The mouse preparation is now running routinely and allows for intracellular recording even in decerebrate unanaesthetised mice during 'fictive locomotion' (Meehan et al., 2012) and transgenic models of amyotrophic lateral sclerosis (Meehan et al., 2010). A summary on this technique was recently published (Meehan et al., 2017).

Jørn Hounsgaard (1948–), MD from Copenhagen University in 1976, started his scientific career with a highly cited study on the presynaptic inhibitory action by acetylcholine in hippocampal slices (Hounsgaard, 1978). Subsequently, he went to New York University to work with Charles Nicholson (in the laboratory of Rudolfo Llinas) and published many articles on the Purkinje cells in the early 1980s. Later he worked with Hultborn on the persistent inward currents (plateau potentials) under in vivo conditions. Several crucial questions needed an in vitro preparation to be able to 'isolate' the motoneurons pharmacologically. This was done in the turtle preparation—with the participation of Ole Kiehn and several guest researchers (most notably the Lithuanian 'connection' with Aron Gutman, Gytis Svirkis, Aidas Alaburda and Robertas Guzulaitis). Much work has focused on the properties of motoneuronal function during activity (swimming/scratching). One recruit to Jørn Hounsgaard's group developed a strong expertise in the study of intrinsic properties in individual neurons (patch clamp recording, pharmacology, two-photon imaging in slice preparations) (see, e.g. Benned-Jensen et al., 2016). They also investigated how astroglia from the spinal cord contribute to motor control (Carlsen et al., 2021; Christensen et al., 2018). In another series of experiments, it was found that serotonin from the raphe nuclei, which is known to increase the motoneuronal activity during exercise, contribute to 'motor fatigue' during very heavy muscular activity by a 'spill-over' of serotonin reaching extrasynaptic receptors that inhibit spike generation (Cotel et al., 2013; Perrier et al., 2018). Together with another recruit, the use of mathematical models of neurons and networks in an interaction with biological experiments was employed to enhance the understanding of the results obtained in classical physiological experiments (Berg et al., 2008).

Jens Bo Nielsen (1962–) soon became the leader of the translational research, investigating the activity and control of transmission in a number of spinal 'reflex' pathways during voluntary movement in man (Crone et al., 1987; Nielsen, 2016; Nielsen & Kagamihara, 1992). Previously, those pathways had 'only' been investigated in anaesthetised animals, thus leaving their function during voluntary movement speculative. He also included electrical and magnetic activation of the corticospinal tract, thus directly testing the excitability of the pathways mediating the voluntary activation of the motoneurons/muscles (Nielsen et al., 1993). Jens Bo Nielsen later became professor at Kiel University (1995–1999) but returned to Copenhagen to become professor at Institute of Exercise, Nutrition and Sport at the Faculty of Science from 2003 (the unit previously called the 'theory of gymnastics'). In 2009, he resumed the relation with the Faculty of Health and Medical Sciences. Leading the group on 'human motor control' at the Institute of Neuroscience. He has made strong contributions to understanding the pathophysiology of motor deficits following brain and spinal cord injury both in adults and in children. Jens Nielsen's laboratory also has a close collaboration with the Elsass institute in Charlottenlund close to Copenhagen (with the focus on cerebral palsy) to obtain a fundamental understanding of the developing brain and the adaptations that occur in relation to early brain lesions

(Herskind et al., 2015; Lorentzen et al., 2017; Willerslev-Olsen et al., 2015). During the years, Jens Bo Nielsen has recruited a large number of younger colleagues.

Ole Kiehn (1958–) started out as a young group leader from 1991, after the early work with Hultborn and Hounsgaard. He decided to focus on the spinal locomotor networks and used the neonatal rat spinal cord preparation, recording from interneurons at different places/segments during fictive locomotion (Kiehn & Kjaerulff, 1996; Kjaerulff & Kiehn, 1996). It was indeed successful, and in 2001, he was offered a group leader position (later professor position) at the Karolinska Institute in Stockholm. There he still focused on the spinal cord, although his focus later extended up to the brain circuits that control the spinal locomotor circuits. He has determined how cellular mechanisms and sub-networks of the spinal cord are involved in pattern formation and the timing and coordination of muscle group activity that give rise to rhythmic locomotor movement (e.g. left–right alternation and extensor–flexor alternation). His work has shown how components of the spinal cord circuit contribute to specific functions of locomotor rhythms and how function arises as a result of interactions between such components. This work is based on the use of modern molecular biological methods for circuit analysis, such as optogenetics and transgenic mouse lines—methods that have allowed him to silence selectively and systematically subpopulations of neurons in the spinal cord to determine the impact on the remaining network (Dougherty et al., 2013). Ole Kiehn has also discovered specific populations of excitatory brainstem neurons (Caggiano et al., 2018) that mediate the episodic control of locomotion: the start and stop of locomotion as well as turning. He has published several important reviews (Kiehn, 2006, 2016). Ole Kiehn subsequently returned to Copenhagen in 2017 as professor in integrative neuroscience at the Department of Neuroscience. He has a large group of collaborators, and he has indeed reintroduced an important field to Danish neuroscience. He received the Lundbeck Foundation Brain Prize in 2022.

Jens Rekling (1960–) was recruited by Mosfeldt Laursen as a pregraduate student in 1986, starting with work on hypoglossal motoneurons in the slice preparation 'transferred' from Oslo several years earlier. Rekling's own developing project was to understand how neurons in small assemblies interact to produce sensory and motor functions in the brain. A variety of electrophysiological and optical techniques are used to study living neurons in preparations of nervous tissue that maintain functional sensorimotor systems under in vitro conditions. Subsequently, he focused on projects addressing respiratory rhythmogenesis (Rekling & Feldman, 1998). En block brainstem, acute slice and slice culture preparations from newborn mice (Phillips et al., 2016) are used to study the cellular and system properties of respiratory neurons with the aim of understanding how breathing rhythm is generated.

5.2.3 | Neurophysiology at Aalborg University: Annelise Rosenfalck moved to Aalborg in 1978

In 1978, Annelise Rosenfalck was appointed Professor at the new Aalborg University, where she founded the Biomedical Engineering Department. The department developed into one of the most dynamic and successful departments in this field in Denmark. She recruited a large number of young researchers as **Steen Andreasen** (already when she was still in Copenhagen), **Lars Arendt-Nielsen** (pain research), **Egon Toft** and **Thomas Sinkjær** (motor control)—all of them now professors with large and active research groups at Aalborg University. However, it is only Thomas Sinkjær and Lars Arendt-Nielsen, who remained within neuroscience. Basic neuroscience at Aalborg University is largely based on Annelise Rosenfalck's foresight and nurture of young gifted students.

Thomas Sinkjær (1958–) and **Lars Arendt-Nielsen** (1958–) subsequently founded the Research group 'Sensory-Motor Interaction' at the Department of Health Science and Technology at Aalborg University. Their work secured a long-lasting support from the National Research Foundation in the period 1993–2006. The work involved basic research in motor control such as reflex control of muscle contraction during walking in humans (Sinkjaer et al., 1988) and basic pain research in humans (Arendt-Nielsen & Yarnitsky, 2009). Translational work includes the development of recording of sensory feedback used to control stimulation of muscle nerves, for example, to control 'drop-foot' pathology following stroke or spinal cord injury (Lyons et al., 2002). Steen Andreassen is since 1998 head of the 'Centre for Model-based Medical Decision Support' at the same department. This centre shall secure the optimal use of the translational research at the university in the healthcare system as well and industry, for example, MUNIN for diagnosing neuromuscular disorders (Andreassen et al., 1996). Lars Arendt-Nielsen founded another centre at the department, the Centre for Neuroplasticity and Pain (CNAP), focusing on experimental tools for provocation and assessment of pain from skin, muscles and viscera in healthy volunteers and pain patients and the development of human biomarkers for the screening/profiling of new analgesics (Arendt-Nielsen & Yarnitsky, 2009). He

was the president of the International Association for the Study of Pain (IASP) in the period 2018–2020. The research presently focuses on translational studies of musculoskeletal pain bridging the gap between basic animal findings and clinical manifestations of pain (Graven-Nielsen & Arendt-Nielsen, 2010; Graven-Nielsen & Mense, 2001).

5.2.4 | Back to the Rockefeller Institute and the work by Torkel Weis-Fogh and Axel Michelsen

Now back to other neuroscience-related activities in the Rockefeller building at the time of Lindhard and August Krogh. Torkel Weis-Fogh (1922–1975) was a zoo physiologist who worked as research assistant in August Krogh's laboratory. They published a classical study on the locust metabolism during and after flight (Krogh & Weis-Fogh, 1951). That led Weis-Fogh to study the aerodynamics of locust flight—and as a follow-up, the physiology of locus flight muscles. He spent a year with Fritz Buchthal at the Institute of Neurophysiology studying twitch contractions of isolated flight muscles, as well as the contribution of the sarcolemma to the force of resting muscles. He then went to University of Cambridge for 4 years, where he discovered a rubbery protein, resilin, on the insect cuticle, while continuing his work on insect flight. He then returned to Copenhagen (became professor of zoophysiology), then went back to Cambridge (in 1966) and became professor of zoology there. In Copenhagen, he had a postdoc named Donald M. Wilson (1932–1970) with his PhD from Theodore Bullock's laboratory at UCLA. From his time in Copenhagen, there are a few scientific reports. The one co-authored with Weis-Fogh is an impressive study on the patterned activity of individual motor units in flying locust (Wilson & Weis-Fogh, 1962). During that work, he also did experiments by himself, demonstrating that the basic flight pattern did remain, even after partial or complete denervation of the sensory input from the wings (Wilson, 1961). As the basic flight pattern thus was independent of the phasic sensory feedback, he concluded that the flight activity was generated by the central neuronal network, later named the 'central pattern generator' (Wilson, 1968). Although this is a fundamental 'breakthrough', it is rarely recognised that the important and original experiments were done at the Copenhagen University.

Axel Michelsen (1940–) is also a zoo physiologist who worked as assistant professor at the Department of Animal Physiology and Zoology at Copenhagen University 1966–1972 **(**Weis-Fogh's laboratory). He defended his doctoral thesis 'The physiology of the locust ear' in 1971 (Michelsen, 1971). He was subsequently appointed professor of biology at Odense University (now the University of Southern Denmark, Institute of Biology, the Sound, Communication and Behaviour Group) where he is still working as emeritus. His field of research covers the biophysics of sound communication, frequency analysis in insect ears, the physics of directional hearing in insects and birds and sound emission in insects. An important part of his work focuses on the 'dance communication' of honeybees (Michelsen, 2003; Michelsen et al., 1986, 1992). His work has been very well recognized internationally, and the group was awarded a 'Centre of Excellence' by the Danish National Research Foundation in the years 1993–2003. Coen Elemans is now the Head of the Sound, Communication and Behaviour Group. With several different laboratories, the fields of research have now diversified and include (i) the filtering away of irrelevant information already at the sensory reception stage; in this field, a focus is on bat echolocation because the bats' active sensing (echolocation) gives unprecedented insight into filtering away irrelevant sound at a very early stage (Jakobsen et al., 2013); (ii) psychophysics to measure the hearing sensitivity of animals secondarily adapted to the aquatic environment who have adapted their hearing abilities to make efficient use of underwater sound cues (Larsen, Wahlberg, & Christensen-Dalsgaard, 2020); and (iii) the function and evolution of the middle ear and directional hearing, mainly in reptiles, amphibians and birds (Christensen-Dalsgaard et al., 2012).

5.2.5 | Establishing neurophysiology at Aarhus University

In the previous section on neuroanatomy, we described the establishment of basic science departments at the newly founded university in Aarhus. **Ingemar Engberg** (1935–2005) was recruited from Gothenburg University to introduce experimental neurophysiology as a research area at Aarhus University. After acquiring the MD degree from Lund University, he was employed at the Department of Physiology, University of Gothenburg, where he was a member of Anders Lundberg's internationally highly recognised research group. His DMSc thesis in 1964 was entitled 'Reflexes to foot muscles in the cat' (Engberg, 1964). He contributed to the main topic of Lundberg's research group, that is, 'the supraspinal control of the spinal cord in the control of movement'. He also developed his own specific interest on the synaptic transmission to motoneurons (Bruggencate & Engberg, 1971; Engberg & Ryall, 1966). In 1972, he was appointed professor at the Department of Physiology,

University of Aarhus, where he expanded his interest in the synaptic control of motoneurons (transmitters, receptors and specific ion channels) (Engberg et al., 1979a; Engberg et al., 1979b; Nedergaard et al., 1987). The focus was on the actions of GABA, excitatory amino acids and monoamines. This area of interest continues until today—and expanded considerably—through his former colleagues and students (e.g. John DC Lambert, John A Flatman and Steen Nedergaard). The experiments on synaptic transmission required superior electrodes and the amplifiers used to record nerve cell signals. Thanks to his interest and talent for electronics and mechanics, Engberg played a very active role in the development of advanced microelectrodes to record signals from individual motoneurons and to apply pharmacologically active substances just outside the individual motoneurons.

At the same time as Ingemar Engberg's employment, Professor Theodor Blackstad (see also above) was establishing neuroanatomy at the Anatomical Institute, at Aarhus University, which meant that neuroscience was strongly represented at the pre-clinical institutes of the Faculty of Medicine.

The line of research described above is still ongoing in Aarhus—presently at the Neurobiology section at the Department of Biomedicine with **Steen Nedergaard** (1960–), **Morten Skovgaard Jensen** (1956–) and **Mogens Andreassen** (1960–). Steen Nedergaard, in close collaboration with Mogens Andreassen, are now focusing their research on the mechanisms behind initiation and spreading of epileptic seizure activity in cortical networks (Mikkelsen et al., 2013). They use various electrophysiological and histochemical techniques and various in vitro animal model systems. Morten Skovgaard Jensen is focusing on the cellular mechanism underlying memory formation (synaptic plasticity) and how neurological diseases affect memory. They use animal models (for Alzheimer's disease, and ischaemia, amyotrophic lateral sclerosis), using in vitro electrophysiology, pharmacology, histology and animal behaviour (Thielsen et al., 2013).

5.3 | Transport between blood and CSF

As described in Chapter 3, the fields of cerebral circulation and blood–brain transfer were reaching highest international recognition both in relation to the development of clinical physiology and in basic neuroscience. In 'basic science', it was **Christian Crone** (1926–1990), and his group at the Department of Physiology, who made a major impact. After Christian Crone graduated as physician from the University of Copenhagen, he started his research career (see Henriksen, 2018). Crone's research dealt with many organ systems. In the field of neuroscience, his first major contribution was the introduction of the tracer diffusion method for investigation of capillary permeability (Crone, 1963). Two tracers are injected simultaneously into the arterial inlet to the organ, and multiple samples are rapidly drawn from the venous outlet. One tracer is an intravascular co-tracer, and the other the test substance whose passage over the capillary is to be investigated. Crone applied the method to several organs including the investigation of the BBB permeability. Among these are remarkable investigations of the glucose transfer across the BBB (Crone, 1965a). He proved that this hydrophilic molecule, essential for brain metabolism, crosses the BBB by a mechanism of facilitated diffusion, that is, a carrier facilitates diffusion in the direction of a concentration gradient. Combining the measurements of the extraction of the test substance with measurement of flow yielded possibilities for calculation of permeability surface areas products ($PS = -F \ln(1 - E)$ where F is the flow and E the extraction = outflow). Later studies dealt with hyperglycaemia and ketone body transport across the BBB. Crone's indicator dilution method was later adapted for clinical use by Lassen and co-workers and used in a series of human BBB studies as described in Chapter 3. Among Crone's other contributions related to neuroscience, his studies on hypoglycaemia should be mentioned. The normal response to hypoglycaemia with a stimulation of the adrenal medulla and release of adrenaline and noradrenaline depend on an intact brainstem. This was shown in studies of decerebrated sheep (Crone, 1965b). In 1976, he first used microelectrodes to determine electrical resistance of capillary walls to ions. This important advance allowed him to formulate the concept of 'leaky' and 'tight' endothelial (Crone & Christensen, 1981; Crone & Olesen, 1982). Christian Crone had several young collaborators, and among those involved in the neuroscience field, the following should be mentioned: **Albert Gjedde** (described in Chapter 3), **Anker Jon Hansen** (1948–2017) and **Søren-Peter Olesen** (1955–). Anker Jon Hansen developed ion-sensitive microelectrodes for use in relation to studies on the brain ion homeostasis (Hansen et al., 1977) and used the microdialysis technology for estimation of ion and transmitter concentrations in the brain tissue (Benveniste et al., 1989). He also determined the dramatic changes in extracellular space and ion concentration during spreading depression (Hansen, 1985; Hansen & Olsen, 1980). He was later (in 1989) headhunted to a senior research position at Novo Nordisk A/S. Søren-Peter Olesen subsequently with great success focused on the ion channels in the heart controlling the normal heart rhythm, as well the pathophysiology of arrhythmia.

Thomas Zeuthen (1946–) got his PhD in 1974 from the Institute of Neurophysiology at Copenhagen University. At this time, his interest focused on ion-selective microelectrode techniques and its use to study the effects of cortical spreading depression (SD) on the extracellular potassium activity (Mayevsky et al., 1974). He subsequently focused on epithelium water transport that could be passive (through the lipid membrane, H_2O channels or cotransport proteins) or active transport. In 1996, he published a book named *Molecular Mechanisms of Water Transport* (Zeuthen, 1996). He aimed at bridging pure molecular biology and cellular physiology. At the time of the publication of this book, his focus has been on the kidney, intestines, retinal pigment epithelium and choroid plexus epithelium. It was actually only when he recruited a PhD student in 1999 (N. MacAulay) that he focused on the mechanisms underlying water and ion homeostasis in the mammalian brain under both physiological and pathophysiological conditions (MacAulay et al., 2004; MacAulay & Zeuthen, 2010). More specifically, the group investigated the transport mechanisms underlying CSF secretion, brain extracellular fluid generation and the pathophysiology seen during spreading depolarisation/depression. The technical approach spans from molecular and biophysical properties of water transport proteins (including aquaporins and cotransporters) to their regulation at the cellular level and their integral function in acutely prepared brain slices and rodent in vivo models. Important reviews of this field have been published (MacAulay, 2021; MacAulay & Zeuthen, 2012).

Maiken Nedergaard (1957–) started her research career in Copenhagen. Subsequently, she moved to New York State where she had appointments for the next decades and finally returned to Copenhagen. Early work of Maiken Nedergaard dealt with spreading depression in stroke and showed that spreading depression is spontaneously and frequently triggered in the periphery of an ischemic infarct. The spreading depression spreads like a wave of vasoconstriction, potassium release, reduced flow and reduced EEG activity in the cortical tissue. It contributes to secondary injury and may increase the infarcted area (Nedergaard & Astrup, 1986).

Glia and calcium signalling became subsequently her main research area through the years. This includes interaction between glial cells and neurons. Glial cells express receptors for neurotransmitters, which induce calcium signalling. She continued this line of work by focusing on propagating glial calcium waves and published the first report demonstrating that astrocytes can signal to neurons and thereby modulate their electrical activity (Nedergaard, 1994). Later studies have illuminated the role of such interaction for pain sensation and epilepsy.

The description in the new millennium of the 'glymphatic system' is a main if not her main contribution to neuroscience (Iliff et al., 2012). The name 'glymphatic system' was coined in recognition of its dependence upon glial cells and the similarity of its functions to those of the peripheral lymphatic system (Iliff et al., 2012). The CSF is produced by the choroid plexi in the cerebral ventricles and flows through the ventricles to the subarachnoid space to be reabsorbed into the bloodstream via arachnoid villi of the dural sinuses, via sheaths along the cranial nerve or through the nasal lymphatics. Classically, the exchange between the CSF and the cerebral extracellular fluid has been considered as a diffusion and multidirectional random bulk flow as consequence of movement, especially induced by cardiac and respiratory function. The new description of the glymphatic system implies that the pulsating waves in the small arterial vessels push the surrounding extracellular fluid into the brain parenchyma and consequently a similar flow from the brain parenchyma back to the CSF takes place along the perivenous space. Thus, the glymphatic system is a polarised fluid transport system in the extracellular space giving much better possibilities for clearance of waste products and exchange with the intracellular fluid than simple bulk flow and diffusion would have allowed. The glymphatic flow is increased during sleep, suggesting that sleep is a restoration phase with increased clearance of waste products from the brain (Xie et al., 2013). Recent studies have further shown that changes in the glymphatic CSF inflow may play a major role in the aggravation of the infarcted area (Mestre et al., 2020). The glymphatic system remains an open field of research (Nedergaard & Goldman, 2020). What is the significance in neurodegenerative diseases, for example, for clearance of amyloid-β and other proteins?

5.4 | Neurochemistry

While the anatomical, physiological and psychiatric subfields of the neurosciences in Denmark had been developed to a significant extent by the second half of the 20th century, neurochemistry as an independent subdiscipline was only at its beginning. As an indication that neurochemistry would become an important part of the neurosciences, *Journal of Neurochemistry* had been launched in 1956, and it should later become not only a leading journal within this discipline, but it was also made the official journal of the International Society of Neurochemistry (ISN), which was created in 1967. Interestingly, the ISN has had two Danish neurochemists among its Council members, Officers and Presidents (see below) during recent years, probably indicating that Danish neurochemistry has a good international reputation.

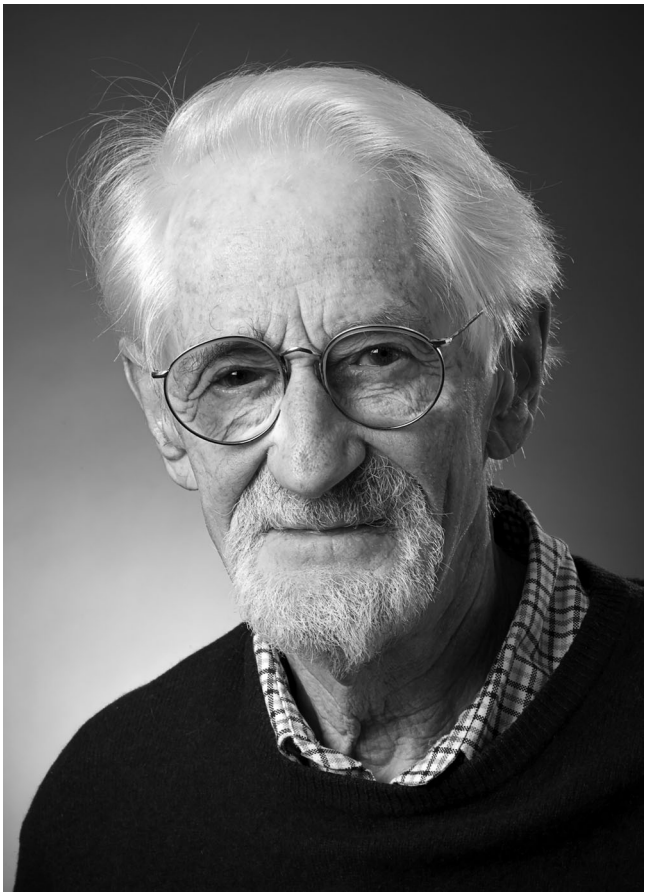

FIGURE 4 Jens Christian Skou around 1997. Photo by Lars Kruse. AU Foto. With permission from Aarhus University.

The first—and outstanding—contributions were made by **Jens Christian Skou** (1918–2018) (Figure 4), who worked at the University of Aarhus. He got his MD degree from Copenhagen University in 1944 and subsequently started his clinical training. He had a liking for surgery, and he prepared to specialise in this field. There was a need for using 'local anaesthetics' as much as possible, and there were questions on their actions, and of how to optimise their use. In 1947, to help his clinical career by earning a doctorate degree, Skou moved to the then very young Aarhus University and its small Department of Physiology. Initially, his work focused on the mechanism of local anaesthetics; the first of seven publications on this topic is from 1954 (Skou, 1954). This brought him to lipid monolayers as models of the nerve cell membrane and then to a research visit to the marine biology research station in Woods Hole, Massachusetts, in 1953. Unlike his small Aarhus department, Woods Hole was a large and dedicated research environment with intense scholar interactions and a huge library of scientific journals and books. This short-lasting trip was a transformative moment of his career. He decided to quit his clinical career plans and to devote himself to research. In 1957, Skou published his first paper on the Na^+/K^+-ATPase enzyme (Skou, 1957). He speculated that the enzyme might be the long-sought sodium–potassium pump that maintains steep electrochemical gradients for Na^+ and K^+ across the cell membrane and enables transmembrane transport and signalling processes, including the action potentials of firing neurons. Further experiments led to additional highly cited publications (Skou, 1960, 1965). Jens Christian Skou received the Nobel Prize in Chemistry in 1997.

Peter Leth Jørgensen (1938–2018) became MD at Aarhus University in 1964. Soon afterwards, he was recruited to the Department of Physiology where Jens Christian Skou was the leader. Peter Leth Jørgensen started to purify the Na^+/K^+ pump (from the mammalian kidney) with a few co-publications with JC Skou (e.g. Jorgensen & Skou, 1971). He established a research group at the department to continue the purification of the pump and resolve its functions in the tubules of the kidney. Further studies with electron microscopy of the purified protein (together with Arvid Maunsbach at the Department of Anatomy) gave the first evidence of structure of the protein (Deguchi et al., 1977; Jørgensen et al., 1982). It seemed to have at least two different structural patterns depending on the binding with either K^+ or Na^+. From 1990 to 2005, he continued his work as professor of molecular physiology at the University of Copenhagen.

Neurochemistry had been essentially absent from the scientific scene at the University of Copenhagen until the mid-1960s at which time **Leif Hertz** (1930–2017) joined the Department of Biochemistry A, University of Copenhagen. Almost at the same time, the Multiple Sclerosis Society had established its own research unit, Institute of Neurochemistry with **Jørgen Clausen** (1931–2004) as its director. This privately run research unit obviously had its scientific focus on myelin disorders and several publications within this field of research originated from this institute during a period of about 10 years after which time the Institute was closed.

Another field of neurochemistry in Copenhagen was related to the biological chemistry of psychoactive drugs, and this discipline was developed at the Institute of Psychochemistry directed by Prof **Ole J. Rafaelsen** (see further in the previous chapter). This institute was part of the University Hospital (Rigshospitalet), and there was a close relationship with the research group of Leif Hertz. Thus, the series of seminars, 'Psychochemical Seminars', at the institute directed by Ole Rafaelsen were often attended by members of the research group of Leif Hertz. Interestingly, the head of the Protein Laboratory. Prof **Elisabeth Bock** (1942–) had started her studies of nervous system specific proteins including neural cell adhesion molecules

(NCAMs) at the Institute of Psychochemistry. Elisabeth Bock developed in the late 1970s a close collaboration with Leif Hertz, collaborative studies also involving **Arne Schousboe** (1944–) who had started as a young biochemist working with Leif Hertz in 1968. Elisabeth Bock later became professor of protein chemistry and developed the Protein Laboratory into an internationally leading institute studying NCAMs and other cell adhesion molecules of importance for brain function. These studies led to numerous important publications, some of which are cited here (Berezin & Bock, 2004; Bock, 1978; Hinsby et al., 2004; Kasper et al., 2000; Kiselyov et al., 1997). She was the first Danish neuroscientist to become an officer and later president of the International Society for Neurochemistry (ISN). This role as one of the officers and presidents of the ISN was some years later taken over by Arne Schousboe who had left the University of Copenhagen to become professor of biochemistry at the Royal Danish School of Pharmacy in 1990.

The research field of Leif Hertz was focused on the role of astrocytes in potassium homeostasis and amino acid-mediated neurotransmission. Leif Hertz was one of the first to demonstrate a depolarization-dependent release of glutamate from brain slices, and it became later generally accepted that this amino acid is the major excitatory neurotransmitter in the CNS. Leif Hertz additionally established facilities enabling determination of oxygen consumption in single cells, and he and his collaborators demonstrated that astrocytes had a high oxidative metabolism, a subject still being a matter of debate. Unfortunately, Leif Hertz encountered serious opposition to his work from influential professors at the University of Copenhagen, who did not like clinical research. This situation eventually led to his decision to leave Denmark in 1974 to assume a position as professor of anatomy, at the University of Saskatchewan in Saskatoon, Canada, and remained at this University until his retirement—a major loss for Danish neurochemistry. Even after his retirement, Leif Hertz remained scientifically active having extensive collaboration with research groups not only at the University of Copenhagen but also at Universities in Australia and China. His year-long collaboration with Danish neurochemists including Elisabeth Bock and Arne Schousboe (see below) lasting for almost 50 years clearly constituted a significant asset to Danish neurochemistry. See Dienel et al. (2023).

The following sections on neurochemistry are organised according to specific themes of research with scientists from 'the new generation' with their main achievements/publications after 1970. The headlines refer to specific themes, or projects, leading to internationally recognised 'breakthroughs'.

5.4.1 | Studies related to glutamate and GABA neurotransmission

As mentioned above, Leif Hertz started a group focusing on neurochemistry at the University of Copenhagen. In 1968, Arne Schousboe, a biochemist and Henrik Lund-Andersen (1945–), at the time a medical student, were recruited as members of the group. Lund-Andersen many years later became a leading ophthalmologist and professor at the University of Copenhagen. As mentioned above, Leif Hertz left the University of Copenhagen in 1974. But prior to that, Arne Schousboe had, at the initiative of Leif Hertz, spent a postdoc period of almost 2 years in the laboratory of Dr Eugene Roberts at the City of Hope National Hospital, Los Angeles, CA, who had discovered GABA as an important amino acid in the brain. Coming back from Dr Roberts, studies related to the function of GABA as well as its precursor glutamate were continued by Leif Hertz and Arne Schousboe, and as pointed out above, these collaborative studies continued for decades after Leif Hertz left Copenhagen.

The studies related to GABA and glutamate-mediated neurotransmission and in particular those directly associated with GABA transporters and receptors led to an association between Arne Schousboe and a pharmacist and medicinal chemist working at the Royal Danish School of Pharmacy, **Povl Krogsgaard-Larsen** (1941–). At the time, Arne Schousboe had worked with Eugene Roberts in Los Angeles, while Povl Krogsgaard-Larsen had spent a postdoc period with the electrophysiologist Prof David Curtis and the biochemist/medicinal chemist Prof Graham Johnston in Canberra, Australia. They demonstrated that GABA receptor and GABA transporter ligands have a chemical structure analogous to that of muscimol isolated from the fly agaric mushroom, *Amanita muscaria*. This turned out to be a major breakthrough in the pharmacology of GABA-mediated neurotransmission. Given that it was the main research interest of Arne Schousboe since he worked with Eugene Roberts, he contacted Povl Krogsgaard-Larsen at the Royal Danish School of Pharmacy. This contact led to several decades of collaborative studies not only related to GABA neurotransmission but also that mediated by the excitatory neurotransmitter glutamate. This was a very active scientific period during which the pharmacological characterization of GABA and glutamate receptors as well as their membrane transporters was undergoing a revolutionary development. In this context, the synthesis of AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazolyl propionic acid) in the laboratory of Povl Krogsgaard-Larsen turned out to be instrumental for understanding the pharmacological diversity of glutamate receptors, and AMPA became one of the most

important pharmacological tools to study this subtype of glutamate receptors (Honoré et al., 1982). Perhaps it would be appropriate in the context also to mention the discovery of a quinoxalinedione (CNQX), an antagonist for these receptors by the research group at the CNS Division of NOVO-Nordisk consisting among others of **Tage Honore** (1951–) and **Jørgen Drejer** (1955–). They had received their PhD from the School of Pharmacy under the supervision of Povl Krogsgaard-Larsen and Arne Schousboe, respectively. CNQX and its analogue NBQX that represented a pharmacological improvement of CNQX became some of the pharmacologically most important tools to study the functional importance of the AMPA subtype of glutamate receptors (Honoré et al., 1988). This became particularly important considering the fact that these antagonists were able to ameliorate the neuronal damage exerted by an excessively high extracellular glutamate concentration in the brain caused by energy failure resulting from stroke-induced ischemia. This so-called excitotoxic effect of an increased extracellular glutamate concentration had been reported previously by others. It was, however, the fundamental observation by **Helene Benveniste** (1959–) that ischaemia led to a significant increase in the extracellular glutamate concentration in the brain, which demonstrated that energy failure and its associated neuronal damage were associated with glutamate excitotoxicity. Helene Benveniste was a medical student working in the laboratory of **Nils Henrik Diemer** at the University of Copenhagen, and she had been using the newly developed technique of placing a thin dialysis tubing in the brain to allow extraction of amino acids from the extracellular space. In the resulting publication (Benveniste et al., 1984), this technology was termed 'microdialysis' and used routinely in all subsequent studies. Helene Benveniste later left Denmark and developed her own scientific career in the United States.

The studies by Povl Krogsgaard-Larsen and Arne Schousboe additionally led to important new developments in the field of GABA neurotransmission. Povl Krogsgaard-Larsen synthesised a number of chemical analogues of muscimol, a natural product that could be extracted from the mushroom *Amanita muscaria*. This included THIP (4,5,6,7-tetrahydroisoxazolo[5,4-*c*]pyridine-3-ol, later named gaboxadol) and THPO (4,5,6,7-tetrahydroisoxazolo[4,5-*c*]pyridine-3-ol), which were selective ligands for the GABA receptors and transporters, respectively. These two GABA analogues should be of fundamental importance for pharmacological characterisation of these entities of GABA-mediated neurotransmission, and they became important for the development of tools to treat, for example, sleep-related problems and epilepsy. Interestingly, **Eddi Meier** (1951–) who had joined the group of Arne Schousboe showed that THIP acted as a neurotrophic agent for the development of cerebellar granule cells and additionally induced a low-affinity GABA receptor in these neurons (Meier et al., 1983, 1984). These studies resulted in a doctoral degree (DSc) for Eddi Meier who some years later left the University to assume a research position at H. Lundbeck.

Further in the context of GABA research, it may be mentioned that another GABA analogue, nipecotic acid, which was found to be a potent inhibitor of GABA transport by Krogsgaard-Larsen and Johnston (1975) (see above) later became important for the development of the first clinically approved antiepileptic drug acting as an inhibitor of GABA transport. The studies leading to this discovery were performed at NOVO-Nordisk by the group led by Claus Bræstrup (see below), and the drug was given the trade name tiagabine. It should be mentioned that the experimental work involved in the development of tiagabine was carried on by **Peter Høngaard Andersen** (1956–) who got his MSc in biochemistry from the University of Copenhagen in 1983 and his DMSc from the same place in 1994 and had joined the group at NOVO-Nordisk working with Claus Bræstrup (see below). The work was published in two important papers (Andersen et al., 1993; Braestrup et al., 1990). Peter Høngaard Andersen later worked at Lundbeck as Head of Research and Development, and after having left Lundbeck in 2013, he became director of 'Innovationsfonden'.

Another important member of the group of Povl Krogsgaard-Larsen was Bente Frølund. In addition to Bente Frølund (see below), a number of younger neuroscientists were educated by Krogsgaard-Larsen, and some of these performed important studies at the laboratory of Prof Bernard Bettler at the University of Basel, and these and other studies led to noteworthy publications (Bräuner-Osborne et al., 2007; Kaupmann et al., 2003).

Bente Frølund (1961–), also working at the Department of Drug Design and Pharmacology, University of Copenhagen, now a full professor, together with Hans Bräuner-Osborne, worked with Prof Povl Krogsgaard-Larsen as a student and onwards. She has primarily been involved in the characterization of receptors and transporters for the neurotransmitters GABA, glutamate and acetylcholine. This has required the chemical synthesis of a large number of structural analogues of these neurotransmitters, chemistry that is often rather complicated. Together with a large number of collaborators in Denmark and abroad, these studies have led to important new knowledge concerning the ways that these transmitter systems govern the signalling in the brain (Frølund et al., 2002).

In addition to the above-mentioned members of the group of Povl Krogsgaard-Larsen, it seems important to mention Prof **Tommy Liljefors** (1941–2015) who for several years played an important role in the molecular characterisation of a number of neurotransmitter receptors including those activated by glutamate and GABA leading to a large number of publications, some of which are mentioned here (Banke et al., 2001; Campiani et al., 2001; Frølund et al., 2000, 2002; Krogsgaard-Larsen et al., 2004).

An important contribution to our current understanding of the mode of action of glutamate receptors was made by **Jan Egebjerg** (1962–). He was educated as MSc and his DSc thesis from the University of Aarhus, and he worked at the Laboratory of Steven Heinemann in San Diego as a member of the group who cloned the glutamate receptors activated by AMPA and kainic acid (Egebjerg et al., 1991; Egebjerg & Heinemann, 1993; Hollmann et al., 1989). He subsequently worked at the University of Aarhus as associate professor in the field of molecular biology. He continued to do important work on glutamate receptors, and part of this research has been published together with Hans Bräuner-Osborne and Povl Krogsgaard-Larsen (Bräuner-Osborne et al., 2000). Since 2019, Jan Egebjerg has had a leading position at the Lundbeck Foundation.

5.4.2 | Monoaminergic neurotransmission

Ulrik Gether (1963–) studied medicine and got his MD in 1990. During his medical studies, he worked in Thue Schwartz's laboratory (Laboratory of Molecular Endocrinology, Rigshospitalet, Copenhagen), which he joined as a research fellow following the completion of his MD degree. In the years 1993–1996, he worked with Brian Kobilka at Stanford University (awarded the Nobel Prize in 2012 for discoveries that reveal the mode of action of G protein-coupled receptors). This stay made Ulrik Gether a neuroscientist! (Gether, 2000). He was an 'Ole Rømer Associate Research Professor' at the Department of Medical Physiology in 1996–2000 and then became professor of neuropharmacology in 2001. Ulrik Gether has long-standing expertise in studying the molecular, cellular and physiological function of monoamine receptors and transporters. The focus now includes (i) the mechanisms controlling activity and availability of monoamine transporters and receptors in the synapse; (ii) how these mechanisms are affected by disease and how they are modulated by drugs; (iii) how genetic variation in monoamine transporters and receptors contributes to diseases characterised by altered monoamine homeostasis; and (iv) genetic mouse models for these diseases. Currently, the main focus of his work is on dopamine and on diseases characterised by dysfunctional dopamine homeostasis such as parkinsonism, ADHD and addiction (Caron & Gether, 2016; Hansen et al., 2014). Ulrik Gether has close collaboration with several younger colleagues as seen from the publications (e.g. Loland et al., 2008; Madsen et al., 2005; Rasmussen et al., 2003).

5.4.3 | DANDRITE

A specific research organisation at Aarhus University, the Danish Research Institute of Translational Neuroscience (DANDRITE), should be introduced at this stage. DANDRITE was established by Lundbeck Foundation and Aarhus University in 2013 and performs interdisciplinary basic and translational research in relation to the brain and the nervous system as a whole. DANDRITE is the Danish node of the Nordic European Molecular Biology Laboratory (EMBL) Partnership for Molecular Medicine, which facilitates collaborative research and access to scientific infrastructure and fosters outstanding international research talent. The EMBL is the leading European institution in molecular life sciences.

The three core leaders at the DANDRITE (Poul Nissen, Poul Henning Jensen and Anders Nykjær) all have a background in biochemistry but have collaborated with many neuroscientists from other fields both within the DANDRITE and their 'home departments', which we will refer to below.

Poul Nissen (1968–) got his MSc in 1993 in chemistry and crystallography. His PhD studies dealt with RNA factors involved in protein synthesis on the ribosome. During his subsequent stay with Thomas Steitz (Nobel laureate in 2009) at Yale, he described the ribosome structure and fundamental mechanisms in protein (Ban et al., 2000; Nissen et al., 2000). Back in Aarhus (in 2000), he returned to the same institute at the Faculty of Science (Molecular Biology and Genetics) where he investigates the molecular mechanisms of membrane transport processes, receptors and bio-membrane ultrastructure. In one study published in 2007 he and his colleagues described the crystal structure of the 'Skou's' Na^+/K^+ pump (Morth et al., 2007). The results of these studies were clinically translated to the development of therapeutics for neurological and psychiatric disorders associated with perturbed ion transport or metabolic control (Poulsen et al., 2010). Another key study achieved in collaboration with both behavioural and electrophysiological expertise at both the Department of Molecular Biology and Genetics and Department of Biomedicine

(Holm et al., 2016) described mutations in the human ATP1A3 gene encoding the neuron-specific Na+/K+-ATPase α3 isoform associated with cognitive deficits.

Poul Henning Jensen (1959–) became an MD in 1989. Following clinical work, he joined the Department of Medical Biochemistry in 1994. There he established the Neurodegenerative Group that focused on Parkinson's disease and related diseases. The group has exploited the strong knowledge generated by clinical genetics and the human genome project to focus on key molecular players in neurodegenerative processes, in particular the gene product α-synuclein (Jensen et al., 1998) and parkin and their up- and downstream pathogenic pathways. This has been done by the use of a broad range of complementary techniques and an extensive network of collaborators (Betzer & Jensen, 2018; Hong et al., 2010). Recently, they have focused on a pathological form of α-synuclein seen in the intestine (duodenum) and in locus coeruleus in Parkinsonian patients. In rats they described that retrograde, and transsynaptic, transport in/from the vagus nerve, possibly contributes to trigger Parkinson's disease (Elfarrash et al., 2019; Van Den Berge et al., 2019). Another group at the Clinical Department of Medicine at Aarhus University has described the decreased risk of developing Parkinson's disease following vagotomy (Svensson et al., 2015).

Anders Nykjær (1963–) became an MD in 1991 and immediately started his PhD studies (at Department of Medical Biochemistry). Research activities are now focused on the functional characterization of a group of type 1 receptors denoted the Vps10p-domain family, or so-called sortilins, that comprises sortilin, SorLA and SorCS-1, SorCS-2 and SorCS-3. The receptors are enriched in neurons where they mediate trafficking and signalling of a vast number of ligands such as neurotrophic factors along with their cognate receptors, neurotransmitter receptors, APP and progranulin. Among many activities, these receptors regulate neuronal cell fate (Nykjaer et al., 2004) differentiation, innervation, synaptic plasticity and learning and memory (Glerup et al., 2016; Richner et al., 2019). They also focus on how genetic variations may contribute to disease development—in particular neuropsychiatric disorders and memory impairment (Blechingberg et al., 2018; Richner et al., 2019).

Centre for Proteins in Memory, PROMEMO, is a spin-off centre of DANDRITE. PROMEMO is presently funded by the Danish National Research Foundation and aims to identify and understand the function of memory-associated proteins that regulates the persistence of a memory, through the use of cutting-edge techniques in proteomics, complex structural biology and optogenetics.

5.4.4 | The benzodiazepine receptor

In relation to the above-mentioned studies of GABA receptors, it should be emphasised that the discovery of the binding site on these receptors of the tranquillising drugs benzodiazepines was done by **Claus Bræstrup** (1945–2023) and **Richard Squires** (1933–) at the Sankt Hans Hospital and the pharmaceutical company Ferrosan. They had obtained radioactively labelled diazepam ([^{3}H] Diazepam) from the manufacturer of diazepam, Hoffmann-La Roche and Co., Basel, and developed a binding assay allowing studies of diazepam binding to membranes isolated from homogenised brain tissue. The results of these studies published in *Science* as well as in *Proceedings of the National Academy of Sciences of the United States of America* (Braestrup & Squires, 1977; Möhler & Okada, 1977) and provided a significant step forward in the knowledge of pharmacological mechanism of action of the benzodiazepines, which prior to this was poorly understood. These results made the GABA receptors an even more interesting pharmacological target, and it facilitated the subsequent purification and cloning of the GABA receptors. Interestingly, Claus Bræstrup was later recruited by NOVO-Nordisk to develop a CNS Division, being active as an independent section at NOVO-Nordisk for several years. In 1989, some of the key scientists at this division decided to create a new biotechnology company by the name NeuroSearch. This group of scientists included the above-mentioned Jørgen Drejer together with other members of NeuroSearch for years and became involved in collaborative scientific projects at the School of Pharmacy as well as the University of Copenhagen.

When NOVO-Nordisk decided to close the CNS Division, Claus Bræstrup shortly after left the Company to assume an important position at Schering in Berlin. Interestingly, he subsequently returned to Denmark to assume the position as CEO at H. Lundbeck and Co., thus strengthening the ties to the Danish neuroscience community.

5.4.5 | Studies aimed at developing escitalopram to treat depressive disorders

In this context, it should be mentioned that the synthetic organic chemist **Klaus Bøgesø** (1947–) at Lundbeck together with others synthesised the compound cipramil/citalopram that turned out to be a highly valuable antidepressant drug inhibiting the serotonin transporter. The racemic form was later separated in its S- and R-enantiomers, and it turned out that the pharmacological action resided in the S-form, leading to the more

specific escitalopram (Hyttel et al., 1992). More detailed studies of the interactions of the R- and S-enantiomers of citalopram at the serotonin transporter revealed that not only is the transporter more sensitive to the S-form than the R-form but additionally the R-form appears to interact with the action of the S-form. This explains why escitalopram is more effective than the racemic drug, and this observation (Sánchez et al., 2004) may well explain why escitalopram became a major selling success for Lundbeck.

5.4.6 | The history of Antabuse

An organic sulphur compound, named tetraethylthiuram disulfide (or disulfiram), was introduced in the rubber industry to accelerate the vulcanisation of rubber. The substance was widely used in the vulcanization of rubber products. It was in connection with the rubber industry that a possible connection between disulfiram and the ingestion of alcohol was first noticed as workers processing tetramethylthiuram disulfide, suffered from nausea when ingesting alcohol (Williams, 1937). The whole history of Antabuse is well described in a large review article (Kragh, 2008a).

Trained as a physician, **Erik Jacobsen** (1903–1985) specialised in biochemistry and worked at Copenhagen University from 1932 to 1934. In 1934, Jacobsen became head of the pharmaceutical company Medicinalco's biological/chemical laboratory, a centre for biomedical research in the Copenhagen area. In the early 1940s, Jacobsen became interested in problems of cell oxidation, which he discussed with **Jens Hald** (1905–1988), a pharmacologist and experienced analytical chemist, who was associated with Medicinalco's laboratory and involved in research on the copper metabolism of intestinal worms. They began exploring the use of disulfiram to treat intestinal parasites. The company had a group of enthusiastic collaborators who, in the course of testing the drug on themselves, accidentally discovered that drinking alcohol while the drug was still in their bodies made them mildly sick. The chemists at Medicinalco A/S developed a new purified form of disulfiram, which turned out to have better pharmacological properties. The company patented it and used that form for the product that was introduced as Antabus (later anglicised to Antabuse) as a treatment of alcohol use disorder (Hald et al., 1948). In Denmark and Sweden, where the drug was approved for medical prescriptions in 1949 (and in the United States in 1951), it was generally looked upon with high expectations. After having served industry in this position for nearly 20 years, Jens Hald was appointed professor of pharmacology at the Royal Danish School of Pharmacy in 1962.

5.4.7 | Establishment of PharmaBiotec Research Centre

In the late 1980s, the Danish government had decided to invest a rather large sum of money to strengthen biotechnological research in Denmark. A group of researchers from the School of Pharmacy and the universities in Aarhus and Copenhagen lead by Povl Krogsgaard-Larsen made an application for a grant from this Biotec Program and managed to get a rather large grant. This formed the start of the PharmaBiotec Research Consortium having Povl Krogsgaard-Larsen and Arne Schousboe as centre directors and a group of leading scientists from the University of Aarhus and the University of Copenhagen such as Jens Zimmer Rasmussen and Nils Henrik Diemer as members. Claus Bræstrup from NOVO-Nordisk also became a member of the Steering Committee. This research centre was active for altogether 8 years and fostered during this period a large number of collaborative scientific projects within the research fields of medicinal chemistry, pharmacology, biochemistry, anatomy and physiology all aimed at understanding the neurotransmission processes of the brain. During the lifetime of the centre, Jens Zimmer Rasmussen moved from Aarhus to Odense to assume a position as professor in neuroanatomy at the University of Odense (later the University of Southern Denmark). The research group of Jens Zimmer focused on establishing an organotypic brain slice culture system, which was successfully used to study excitotoxicity, a topic of considerable interest to the groups in Copenhagen working on glutamate receptors. Jens Zimmer brought his close collaborator Bente Finsen from Aarhus to the University of Southern Denmark, and Finsen later got a professorship and made important contributions to understand the role of microglia in development of neurodegenerative diseases such as Alzheimer's disease.

Nils Henrik Diemer, another prominent member of the PharmaBiotec Research Centre working at the Institute of Neuropathology, University of Copenhagen, was also awarded a professorship while PharmaBiotec was still active. As pointed out above, Diemer has been instrumental in providing evidence that ischemia would lead to an excessive release of glutamate to the extracellular space in the brain causing excitotoxic neuronal damage, thus firmly implicating glutamate in this condition.

Another important activity initiated during this period was the introduction of nuclear magnetic resonance (NMR) spectroscopy to study metabolic pathways in cultured neurons and astrocytes using ^{13}C-labelled substrates. This technology had not previously been used to study neural cells in culture due to its limitations regarding sensitivity. However, a collaborative study with

Ursula Sonnewald (1952-) at the University of Trondheim demonstrated that astrocytes but not neurons were able to synthesise and release citrate (Sonnewald et al., 1991). This process requires the anaplerotic enzyme pyruvate carboxylase, which had previously been shown to be expressed selectively in astrocytes (Yu et al., 1983). The significance of the astrocyte-specific expression of pyruvate carboxylase has been discussed in a recent review (Schousboe et al., 2019). The metabolic studies in cultured neurons and astrocytes initiated by Ursula Sonnewald were continued successfully by **Niels Westergaard** (1960–) who joined the PharmaBiotec group shortly after its establishment. He was responsible for a large number of publications on glutamate and citrate metabolism (Sonnewald et al., 1993, 1997; Westergaard et al., 2017), thus continuing the work initiated by Ursula Sonnewald. Niels Westergaard got his PhD in 1992 and his doctoral degree (DPharm) in 1997. He decided to leave the university environment to assume a research position at NOVO-Nordisk.

5.5 | Cognitive neuroscience

Cognitive neuroscience is the scientific field concerned with the study of the biological processes and aspects that underlie cognition, with a specific focus on brain connections involved in mental processes. Cognitive neuroscience is a branch of both neuroscience and psychology, overlapping with disciplines such as behavioural neuroscience, cognitive psychology, physiological psychology and affective neuroscience. Cognitive neuroscience relies upon theories in cognitive science coupled with evidence from neurobiology and computational modelling.

In the present section, we describe the evolution of the basic/clinical aspects of cognitive neuroscience, which complements the description of the evolution of clinical psychology provided in Section 4.

Alfred Lehmann (1858–1921) was the pioneer of experimental psychology in Denmark (see Pind, 2019). He was educated as an engineer and spent the winter of 1885–1886 in Wundt's laboratory in Leipzig. Upon his return to Copenhagen, he established the Laboratory of Psychophysics, one of the oldest laboratories of psychology in the world. At the outset of his scientific career, Lehmann focused mainly on the bodily correlates of mental states, emotions in particular. He was an early critic of the James–Lange theory of emotions.

Claus Bundesen (1948–) and **Axel Larsen** (1944-) are now emeriti professors of cognitive psychology at the Department of Psychology, University of Copenhagen. Bundesen's theory of visual attention is a mathematical (computational) theory that specifies how visual objects compete for entry into visual short-term memory (VSTM). The theory has been developed and tested over several decades by Bundesen and co-workers (Bundesen, 1990; Bundesen et al., 1984; Larsen, Markussen, & Bundesen, 2020; Shibuya & Bundesen, 1988) and now encompasses a systematic neurophysiological interpretation of its key concepts (Bundesen et al., 2005; Bundesen & Habekost, 2008). The theory of visual attention accounts for a broad range of normal attentional phenomena (Vangkilde et al., 2012) and has been used with considerable success in describing attention disturbances (Vangkilde et al., 2011).

A classical problem in visual object recognition concerns how we can determine whether two or more objects in the visual field share a common shape irrespective of their size (or orientation). For the case of size, Larsen and Bundesen proposed a new solution in two widely cited papers (Bundesen & Larsen, 1975; Larsen & Bundesen, 1978). Essentially, that one object by a time-consuming process may be encoded and transformed in VSTM to fit the size or orientation of another visual object. Extending these studies, they developed computational models for how we may achieve size and orientation invariance (Larsen, 2014; Larsen et al., 1999).

Other studies (summarised in Larsen & Bundesen, 2009) have revealed how size invariance in object recognition in part seems to be based on the processes by which we perceive moving objects. In line with these results, Larsen and co-workers showed that brain structures (visual area V5/MT) that are strongly involved in visual motion processing are also activated in tasks where observers are requested to determine if two objects are identical except for size (Larsen, Markussen, & Bundesen, 2020). The field is developing, with several investigators of the 'next generation' having a strong impact both at the same department in Copenhagen and also at the University of Southern Denmark (Gerlach et al., 2002; Kyllingsbaek, 2006; Starrfelt & Gerlach, 2007).

Ivan Divac (1932–1999) was an anatomist/physiologist who studied defects in higher cognitive functions in animals following specific brain lesions—thus he represents the 'physiological' part of 'cognitive neuroscience'. He was born in Yugoslavia and graduated as MD from Belgrade University in 1959. He stayed in the Department of Pathophysiology there for a few years, but the possibilities for research were very limited. He then got a scholarship for studies at NIH, Bethesda, for 1963–1964 with Enger Rosvold and Maria Szwarcbart as his mentors. The outcome of that stay was a high-impact publication on the behavioural effects of lesions of the caudate nucleus with bilateral connections with the

inferotemporal and orbital frontal cortex in monkeys—both involved in higher cognitive functions (Divac et al., 1967). He then went to the Nencki Institute in Warsaw (1955–1957, by invitation of Jerzy Konorski), and pursued similar work in monkeys, cats and rats using delayed alternation and visual discrimination as behavioural tests. He then went for 2 years to Pennsylvania State University, at the laboratory of J. Michael Warren. He then was recruited to the Department of Neurophysiology at Copenhagen University where he later became associate professor. At his arrival, he visited the Department of Psychology and invited interested scientists to participate in weekly seminars, which resulted in prolonged experimental collaboration with **Anders Gade** (1946–), subsequently associate professor at the Department of Psychology. **Jesper Mogensen** worked in Ivan Divac's group in 1985–1990, and at the end of this period, Gitta Wörtwein (1966–) from Germany joined the group and is presently one of the co-leaders of the Laboratory of Neuropsychiatry. Jesper Mogensen later became associate professor of psychology (since 1998; see further below). Ivan Divac maintained a broad international network until his premature death in 1999.

Jesper Mogensen (1954–2022) was professor at the Department of Psychology, University of Copenhagen, since 2011. He was the founder and head of the Unit for Cognitive Neuroscience (one part of the large research centre named 'Cognition and Neuropsychology' described above in relation to Claus Bundesen and Axel Larsen), and he was director of the Research Centre for Brain Injury Rehabilitation. His early work with Ivan Divac includes a description of the connections and functions of neostriatum and comparable areas to prefrontal cortex in pigeons (Mogensen & Divac, 1982). His focus has involved neurocognitive organisation and reorganisation of the normal and injured brain and also include relevant animal models (Wogensen et al., 2015).

Per Roland (1943–) received his MD and PhD from the University of Copenhagen in 1970 and 1987, respectively. His first publications related to the proprioceptive inputs from muscle for sensations of tension and of kinesthesia (Roland & Ladegaard-Pedersen, 1977), This was followed by several publications from NA Lassen's group at Bispebjerg, some of which tend to extend into the 'cognitive' field, that is, the mapping of cortical areas activated by thinking (Roland & Friberg, 1985). This became even more obvious during his stay at the Clinical Neurophysiology, the Karolinska Institute in Stockholm (Kinomura et al., 1996), and his subsequent stay at the Nobel Institute for Neurophysiology at the Karolinska Institute, where he investigated the organisation of neuronal activity and field potentials following visual stimulation in animals (Roland et al., 2006; Roland & Gulyás, 1994). Since his return to Copenhagen in 2011, Per Roland and colleagues examine the space–time dynamics in the cerebral cortex, that is, the progression of membrane current changes, local field potential changes and spiking in the space made up of the cortical network of neurons with the purpose of finding principles of cortical mechanisms of higher visual analysis (Roland, 2017).

Mammalian brains produce perception, thoughts and behaviour over a wide spectrum ranging from a reflex to theory of relativity. So far, explanations on how brains may produce perceptions, thoughts or behaviour relied on experimental results showing temporal dynamics of spiking activities and brain models explaining aspects of temporal dynamics of spiking and membrane conductance. Recently, the journal *Neuron* published a special issue on 'How Does the Brain Work' emerging from a workshop that took place at the Carlsberg Academy in Copenhagen in September 2016 (*Neuron*, 2017). The participants of this workshop—from both experimentalists and theoreticians—explored current brain theories and discussed their ideas for how the brain might work—certainly an expression of 'cognitive neuroscience'.

Under the broad title of 'cognitive neuroscience', it seems reasonable to include the field of phenomenology, philosophy of mind and cognitive science, which are the topics of the 'Centre for Subjectivity Research' at the Faculty of Humanities at Copenhagen University. The centre was initiated by **Dan Zahavi** (1967–), professor of philosophy, **Arne Grøn** (1952–), professor of ethics and philosophy of religion, and **Josef Parnas** (1950–), professor of psychiatry, all at the University of Copenhagen. The National Research Foundation funded this centre in the period 2002–2012 (Danish National Research Foundation: Center for Subjectivity Research, n.d.). After the end of the funding in 2012, the centre has continued its research with support from a variety of both Danish and European public and private foundations. Much effort has been invested in promoting the dialogue between philosophy and empirical science, in particular psychiatry and psychopathology, but also clinical psychology, cognitive science and developmental psychology (Sass & Parnas, 2003; Zandersen & Parnas, 2019). Over the years, the centre has worked systematically on topics such as intentionality, imagination, empathy, action, perception, embodiment, naturalism, self-consciousness, self-disorders, schizophrenia, autism, normativity, anxiety and trust. **Dan Zahavi**'s writings have dealt extensively with topics such as self, self-consciousness, intersubjectivity and social cognition (Zahavi, 2008, 2015).

6 | CONCLUDING REMARKS

The first Danish neuroscience at an international level originate from the 17th century—Thomas Bartholin, Nicolaus Steno and Jacob Benignus Winsløw. The basic education for all of them started at the University of Copenhagen, but for the last two persons, the major scientific contributions were made in other European countries. Although the University of Copenhagen certainly supported research during the centuries from its foundation in 1479, neuroscience was very much related to the medical profession and was not one of the areas priorities in the beginning. The continuation of neuroscience research was certainly closely linked to the major hospitals during the 19th and the first half of the 20th centuries. At the second half of the 20th century (or even just before the Second World War), the university started to build an important profile within basic medical research, but neuroscience was rather late in comparison to other fields. When the basic medical science started to achieve international strength and recognition, first the research in Copenhagen, and soon also of Aarhus University, and subsequently Odense (the University of Southern Denmark) and then Aalborg. The research was very much related to the teaching of medical students, and naturally a close relationship with the main hospitals continued—translation research has been one of the strengths in Danish neuroscience.

In the Preface, we argued that the 'history' in the present article ended by scientists and projects that had been established latest by the very end of the 20th century. We have followed up these specific areas describing research projects and publications. We have thus avoided an unwanted evaluation of 'ascending' young scientists. Fortunately, the Danish Centre for Studies in Research and Research Policy at Aarhus University and the Lundbeck Foundation recently published a mapping of the international impact of Danish Neuroscience from 2004 to 2015 (Andersen et al., 2018). The purpose was to assess the standing—using tailored scientometric methodology—of Danish neuroscience in relation to a number of world leading neuroscience countries. The analysis shows that Danish neuroscience is doing well in terms of publication output and impact.

AUTHOR CONTRIBUTIONS

All three authors have contributed to the conceptualization of the project and to all parts of the manuscript. Arne Schousboe has specially dealt with neurochemistry, Hans Hultborn with other aspects of basic neuroscience and Olaf B. Paulson with the clinical aspects.

CONFLICT OF INTEREST STATEMENT

All authors have no conflict of interest.

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Olaf B. Paulson[1,2]
Arne Schousboe[3]
Hans Hultborn[4]

[1]*Neurobiology Research Unit, Department of Neurology, Rigshospitalet, 9 Blegdamsvej, Copenhagen, Denmark*
[2]*Department of Clinical Medicine, University of Copenhagen, Copenhagen, Denmark*
[3]*Department of Drug Design and Pharmacology, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark*
[4]*Department of Neuroscience, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark*

Correspondence
Olaf B. Paulson, Neurobiology Research Unit, Department of Neurology, Rigshospitalet, 9 Blegdamsvej, DK-2100 Copenhagen, Denmark.
Email: olaf.paulson@nru.dk

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