Neuropathology in Pitié-Salpêtrière hospital: Past, present and prospect

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Abstract

Pitié and La Salpêtrière, both founded in the17th century, were for long two distinct hospitals until they merged in 1964. The name La Salpêtrière is inherited from the initial purpose of the buildings designed to produce saltpeter for gun powder. But the place was soon transformed into an asylum to shelter the poor and the insane. From the care of this underprivileged population, alienists such as Pinel have paved the way for modern medicine for the mentally ill at the time of the French Revolution. In the second half of the 19th century, Jean-Martin Charcot and his students laid the foundations of modern neurology from the observation of the large population hosted in La Salpêtrière, mostly women with severe chronic diseases. Charcot led clinic-pathological studies in about all the fields of nervous system disorders. His successors (including Raymond, Dejerine, Pierre Marie) maintained the same close relationship between clinical neurology and neuropathology. In parallel with the development of neurosurgery at Pitié hospital, neuropathology first spread through small laboratories attached to clinical departments. The merger of the two hospitals in the early sixties coincided with the creation of a large university hospital in which the care and study of diseases of the nervous system were preponderant. An independent laboratory of neuropathology was created, led by Raymond Escourolle. This period was on the eve of important developments in neuroscience around the world. Today, the Pitié-Salpêtrière neuropathology laboratory still plays a central role between neurology and

neurosurgery clinics and major research institutes such as the Brain Institute (Institut du Cerveau et de la Moelle, ICM) and the Institute of Myology.

Introduction

The development of neuropathology has been closely related to the development of neurology and is now part of neurosciences. Pitié-Salpêtrière hospital has offered early in its history a favorable ground to the emergence of an interest in nervous system diseases and has hosted precursors in these fields. This tradition continues with permanent interactions between clinical neurology, applied neurosciences and leading research institutes, such as the Brain institute (Institut du Cerveau et de la Moelle, ICM) and the Institute of Myology.

Context of the rise of neurological sciences at Pitié-Salpêtrière

Interest in the pathology of the nervous system appeared in Paris in public hospitals designed to accommodate low-income populations. Since the Middle-Ages, Augustinian Christian nuns watched over the health of the poor at the Hôtel-Dieu Hospital, at the foot of Notre-Dame Cathedral, in the heart of the city. In the 15th and 16th centuries, during the Renaissance period, the Parisian population increased considerably, reaching 400,000 people, 70% of whom were poor or at risk of becoming so [1].

At that time, religious institutions began to lose part of their hegemonic influence and king Francis I of France decreed the founding of the Great Office of the Poor "*for the relief of the poor and the decline of begging in Paris"*. The first Pitié hospital was then built near the Royal Garden, known today as the Jardin des Plantes [2].

Twenty-five years later, outside the city, a former gunpowder factory producing saltpeter (*salpêtre* in French), was turned into a hospice. It was the origin of "La Salpêtrière". However, all this was

not enough because the number of poor was constantly increasing. Their image evolved in society, in which they were increasingly perceived as immoral and dangerous [3]. The young king Louis XIV then promulgated the Great Confinement (*Grand Renfermement*) of the poor and ordered the building of large hospices to house them: La Salpêtrière for women and Bicêtre, south of Paris, for men [4]. Throughout the 18th century, La Salpêtrière looked like a prison, while the old Pitié included a maternity ward and an orphanage. At the beginning of the 20th century, the old Pitié was destroyed and rebuilt next to La Salpêtrière. In 1964, the two hospitals merged resulting in the creation of the university hospital Pitié-Salpêtrière [2].

Parallel development of neurology and neuropathology

How did the neurological sciences develop in this context? Some women had been admitted at La Salpêtrière because of behavioral disorders. During the French Revolution, at the end of the 18th century, Philippe Pinel, both a physician and a politically engaged citizen, was appointed as an alienist in La Salpêtrière. He became famous by ordering the removal of the chains from women with mental illness. With the help of his student Esquirol, he wrote clinical medicine treatises for the stated purpose of delivering a "more precise and more accurate" description of mental diseases and was later credited for being one of the founders of medical psychiatry [2].

But the real beginning of neurology dates back to 1862, when two young men, Alfred Vulpian and Jean-Martin Charcot were appointed at La Salpêtrière [5]. Together, they accurately described the tremor of multiple sclerosis as opposed to the tremor seen in *paralysis agitans*, re-named Parkinson's disease by Charcot during his lessons [6][7][8]. Vulpian left La Salpêtrière for La Charité Hospital, since then replaced by the Saints-Pères faculty of medicine. Charcot developed in La Salpêtrière what was then named neurology and published groundbreaking works in several areas of neurology and neuropathology, such as multiple sclerosis [9], vascular diseases with Charcot

and Bouchard aneurysms [10], degeneration of peripheral nerves, and of course amyotrophic lateral sclerosis, also known as Charcot's disease [11][12].

His approach based on clinical observation supplemented by an anatomical analysis [Figures 1-3], was inseparable from his teaching [Figure 4]. His reputation attracted many students. One of his main interests was the mechanisms of hysteria, as illustrated by the famous painting "A clinical lesson at La Salpêtrière" [13]. He is represented commenting on the condition of one of his patient, Blanche Wittman, supported by Joseph Babinski [14]. Among the students, stand future big names like Gilles de La Tourette, Bourneville, Paul Richer (who became also a famous sculptor), Brissaud [Figure 5], Pierre Marie and the son of Charcot, Jean-Baptiste, better known as navigator and explorer. Foreign students were also attracted by Charcot's teaching. Among them, the young Sigmund Freud of Vienna, who developed an interest in hysteria from his stay at La Salpêtrière during the winter 1885, giving up his previous activity of neuropathology [15][16]. In 1892, Kinnosuke Miura, founder in 1902 of the Japanese Society of Neurology and considered the precursor of neurology in Japan, stayed at La Salpêtrière [17]. Among other students of Charcot known for their important work in neuropathology, were those who worked on Parkinson's disease, after Charcot and Vulpian. Paul Richer modeled a famous statuette representing an old woman: "*Attitude and facies in Parkinson's disease, after a patient of La Salpêtrière*". Based on an observation made by Blocq and Marinesco, Brissaud emphasized the role of *substantia nigra* in Parkinsonism [18] [19] [20]. Later, in 1919, Tretiakoff, a Russian medical student who wrote his thesis at La Salpêtrière under the supervision of Pierre Marie, gave the name of "Lewy bodies" [Figure 6] to the inclusions initially described by Friedrich Lewy [19] [21][22].

Pierre Marie (1853-1940) was one of the most prolific among the disciples of Charcot. He left important contributions in the fields of neurology and rheumatology. He described Charcot-Marie amyotrophy [Figure 7], acromegalia, hypertrophic paraneoplastic osteoarthropathy, cerebellar

heredo-ataxia, cleidocranial atrophy and rhizomelic spondylosis [23]. Pierre Marie's cerebellar heredo-ataxia was to be distinguished from Friedreich ataxia (in which tendon reflexes were abolished): the former was to be considered a disease of the cerebellum when the latter was thought to be due to lesions involving the spinal cord. The type of hereditary cerebellar atrophy that Pierre Marie actually described has been discussed. T. Uchihara, examining an old post mortem case from La Salpêtrière concluded that it must have been a case of what is known today as SCA3 [24].

Pierre Marie is also famous for challenging Broca's hypothesis about aphasia, published 40 years earlier from observations made in Bicêtre Hospital. Pierre Marie claimed that aphasia was due to a lesion of what he called a *quadrangle*, including basal ganglia and deep white matter [25]. Jules Dejerine, a former student of Vulpian, had adopted the notion established by Broca of the key role of the foot of the third frontal convolution. The rivalry between the two men only worsened between 1883 and 1906, with peaks of tension such as this challenge to a duel in 1892 which fortunately did not take place. Dejerine was working closely with his wife, Augusta Dejerine-Klumpke, who was an excellent anatomist and a neuroscientist [Figure 8]. Based on a horizontal section, taken higher than the one illustrated by Pierre Marie, Mrs Dejerine demonstrated that the section on which he based his reasoning actually passed below the plane of the third frontal convolution responsible for aphasia and that his *quadrangle* included actually degenerating association pathways in the underlying white matter [26] [27] [28]. In 1911 Dejerine obtained the Chair of neurology in La Salpêtrière, whereas Pierre Marie was appointed to the Chair of pathology. Pierre Marie succeeded to Dejerine after his death in 1917. All former collaborators of Dejerine including Augusta Dejerine-Klumpke, were asked to leave the department of neurology. She had to remove all Dejerine's archives, which are now hosted at the Dupuytren museum of

anatomy at Sorbonne University [29]. A recent conference at La Salpêtrière organized in tribute to Jules Dejerine underlined the extent and depth of his work [28][30].

Charles Foix (1882-1927) worked with Pierre Marie heading the laboratory at La Salpêtrière [23]. After he spent part of the First World War in Greece as a medical doctor in the French Army of the Orient, he was appointed to the ward of chronic patients in the hospice of Ivry-sur-Seine, near Paris (now Charles-Foix Hospital), where he led an impressive number of studies, especially on the basal ganglia and the cerebrovascular system. He was expected to succeed Guillain at the Chair of Neurology at La Salpêtrière but his promising career was soon interrupted by his early and unexpected death at the age of 44 [31].

Joseph Babinski (1857-1932), one of Charcot's closest students, was a talented semiologist. He is world-renowned for the "Babinski sign" that he described in 1896 as an extension of the great toe after sole stimulation in patients with a lesion of the pyramidal tract [32]. He was head of a medical department at Pitié hospital, where he developed the first neurosurgery unit in France, in collaboration with Thierry de Martel (1875-1940) and Clovis Vincent (1879-1947) [23] [33] [34]. Another department of neurosurgery was founded in La Salpêtrière after the Second World War [34].

Starting in the 1930s, neuropathology, which until then had been an integral part of clinical practice, was gradually handed over to specialist practitioners. Each department had its own laboratory specialized in *post mortem* brain studies or more oriented towards muscular pathology, study initiated by Professor Raymond Garcin, followed by his students Jean Lapresle and Michel Fardeau [35]. The laboratories associated with the neurosurgery departments were dedicated to tumor pathology: one in Pitié run by Henri Berdet followed by Roger Messimy, Jean Racadot and Jacques Poirier; the other in La Salpêtrière run by Jean-Emmanuel Gruner followed by Jean-François Foncin. Ivan Bertrand (1893-1965), who led the laboratory of the nervous system clinics

for nearly 40 years, had been first trained in histology. He had come to neuropathology under the influence of Gustave Roussy and Pierre Marie and worked in collaboration with G. Guillain, T. Alajouanine, P. Castaigne and many others [36].

The merging of Pitié and Salpêtrière in 1964 into a large university hospital gave a new impulse to the care and study of nervous system diseases to which a new building was dedicated [37]. The neuropathology department was included in the building in close relationship but independent from the neurology clinics [Figure 9]. The head of the new laboratory was Raymond Escourolle, a neuropsychiatrist, former student of Théophile Alajouanine and Jean Delay. In Sainte-Anne psychiatric hospital, he had met another young neurologist and psychiatrist, Serge Brion, trained in neuropathology in Harry Zimmermann's laboratory at Montefiore Hospital in New York [38]. Starting from this partnership, Raymond Escourolle initiated a renewal of neuropathology at Pitié-Salpêtrière hospital. The laboratories formerly attached to neurology and neurosurgery merged into the Department of neuropathology, which in 1985 was named after Raymond Escourolle [Figure 10]. His successors, Jean-Jacques Hauw, then Charles Duyckaerts, have developed research and national networks especially in the fields of prions and neurodegenerative diseases and created the conditions for a multi-purpose laboratory including all areas of neuropathology in adults.

Present and prospect: neuropathology and neurosciences

Neuropathology is as ever at the interface with neurology and neurosurgery, to which one should add today neuroscience that has won academic authority and for which Pitié-Salpêtrière hospital offers a rich environment. The foundation of the Brain Institute (ICM) in 2005, preceded by that of the Institute of Myology in 1996, confirmed the dynamism of neuroscience on the site. Since 2012, the neuropathology laboratory has been organized into three units: neurosurgical pathology;

muscle and nerve pathology; autopsy and pathology of neurodegenerative and prion diseases. The three units work together and in close relationship with the surrounding research teams.

The department of neuropathology at Pitié-Salpêtrière has become the only adult medical autopsy center in Paris area. Its activity now accounts for nearly 30% of medical autopsy requests in France. This competence was maintained and developed first to ensure diagnosis of neurological diseases. Systematic analysis allows the Department of Neuropathology to be at the forefront of the detection and monitoring of new diseases or new forms of previously known disorders. It played a key role in distinguishing different types of AIDS encephalopathies and of prion diseases [39] [40]. The study of the latter was facilitated by the national network for neuropathological monitoring of Creutzfeldt-Jakob disease (CJD), created by Jean-Jacques Hauw with the support of the French health agency (Institut de Veille Sanitaire, InVS). This network aims to collect samples of all cases in which the diagnosis of Creutzfeldt-Jakob disease had been made and which have been autopsied on the French territory. The department of neuropathology is now involved, in collaboration with the Pasteur Institute, in the identification of emerging virus encephalitides, combining New Generation Sequencing (NGS), immunohistochemistry and *in situ* hybridization [41]. The NeuroCEB biobank, developed by Charles Duyckaerts ten years ago, runs a national brain donation network. Patient associations have financially supported the creation of the brain bank and now provide help to all phases upstream of brain donation: from initial information to the *post mortem* transport of the body. The current member associations give support in the following neurological disorders: Parkinson's and Alzheimer's diseases, multiple sclerosis, motor neuron disease, frontotemporal lobar degeneration and ataxia. This platform is an essential tool for carrying out research in neurodegenerative pathology. Correlation between genetics and histopathology is now one of the main topics in the neuropathology of degenerative diseases. Junko Takahashi [42], Takahiro Takeda [43] [44] [45] and Yuichi Riku [46] have explored

this field in amyotrophic sclerosis and frontotemporal dementia, during their stay in La Salpêtrière. Seeding and propagation of misfolded protein is a major topic of interest that Charles Duyckaerts explored at first with the collaboration of Toshiki Uchihara [47]. They started with the observation of a small part of cortex, disconnected after neurosurgery, in an Alzheimer's disease patient. In this cortex A-β pathology was present but not tau pathology suggesting that the propagation of A-β may occur independently of innervation. Since then, other evidence came from patients who developed CJD after treatment by cadaver-derived growth hormone [48][49]. A recent observation made after post-traumatic *dura mater* grafting, without CJD, suggested a nearly 45 years long incubation of the amyloid seeds, leading finally to a devastating amyloid angiopathy without tau pathology [50] .

The evolution of knowledge is particularly rapid in the field of neuro-oncology. Pathological analysis plays a major role in research on brain tumors to provide tumor models, select samples for innovative analyses, and validate, with *in situ* methods, hypotheses on cellular and molecular mechanisms. The central nervous system is characterized by wide cell diversity, involved in the patterns of regional differentiation during normal development. This diversity is also involved in a large number of tumor types as emphasized by methylation studies. An example of the close relationship between cell types and molecular profiles has been shown in chordoid gliomas of the third ventricle [51]. This rare tumor always expresses a missense mutation of the gene encoding a proteinase K (PRKCA). Substrate analysis of this enzyme opens up targeted therapeutic perspectives [52]. Metabolic studies offer other perspectives: oxidative metabolism is increased in glioma cells with a FGFR3-TACC3 fusion and treatments directed against oxidative stress like metformin can induce tumor cell death [53][54].

Muscle biopsy is still mandatory for the diagnosis of vasculitis and amyloidosis. But it is also necessary for the diagnosis and research in heterogeneous groups of diseases such as necrotizing

myopathies or dermatomyositis [55]. A collaborative work with Akinori Uruha showed that an interferon inducible molecule, myxovirus resistance protein A, was a reliable marker of dermatomyositis [56]. In addition, muscle biopsy allows the identification of new entities, such as severe inflammation of the muscle in which the reaction of T lymphocytes is predominant. This kind of myositis is observed in patients treated with immune checkpoint inhibitors, used against cancer to improve the T cell response [57]. Muscle biopsies also identified late onset sporadic nemaline myopathy, found in patients with monoclonal gammapathies (MGUS) [58].

Conclusion

Although neuropathology is not recognized in France as a primary specialty, unlike in other countries in Europe and America [59], Pitié-Salpêtrière laboratory remains a pivot between neurology, neurosurgery, pathology and neuroscience. This privileged situation gives it national and international visibility. The resulting attractiveness and the welcoming of students and colleagues from all over the world are at the center of its missions. Due to its close relationship with the Institute of Myology and the ICM, it is fully in keeping with an unbroken tradition of 230 years of neuroscience studies.

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Legends of the figures

Figure 1. Tear (k) of the outer wall of an aneurysm (Charcot-Bouchard aneurysm). Drawing by JM Charcot circa 1866 in the album “Pathological Anatomy, Charcot Museum”. Collection of the Department of Neuropathology Raymond Escourolle, Pitié-Salpêtrière Hospital.

Figure 2. Border of a plaque of multiple sclerosis. Chromic acid impregnation technique. Drawing by JM Charcot circa 1868 in the album “Pathological Anatomy, Charcot Museum”. Collection of the Department of Neuropathology Raymond Escourolle, Pitié-Salpêtrière Hospital.

Figure 3. Bilateral degeneration of cortico-spinal bundles in medulla and spine at cervical, thoracic and lumbar levels in a case of amyotrophic lateral sclerosis. Drawing by JM Charcot circa 1870 in the album “Pathological Anatomy, Charcot Museum”. Collection of the Department of Neuropathology Raymond Escourolle, Pitié-Salpêtrière Hospital.

Figure 4. Charcot in the autopsy amphitheater at La Salpêtrière wearing clogs and a top hat. Pen drawing by his student Edouard Brissaud. From the New Iconography of La Salpêtrière Coll., Paris: *Prog Med* 1875.

Figure 5. Edouard Brissaud in the histology laboratory of the neurological clinics of La Salpêtrière circa 1895.

Figure 6. Tretiakoff C. Thesis, University of Paris, 1919. Chart IV (Fig. 9): *Intra-cellular inclusions or "Lewy bodies"; Bielschowsky's method.* pi.n : black pigments (*pigments noirs*). Nc: nucleus. Collection of the Department of Neuropathology Raymond Escourolle, Pitié-Salpêtrière Hospital.

Figure 7. Marinesco, MG. Contribution to the study of Charcot-Marie amyotrophy. *Arch. Med Exp Anat Pathol* (Paris) 1894. Chart XVII showing muscle atrophy (Fig.1); median nerve atrophy (Fig.2); degeneration of the anterior horn at the cervical level (Fig. 6, 7, 8).

Figure 8. Jules Dejerine and Augusta Dejerine-Klumpke around 1900.

Figure 9. The new laboratory of neuropathology in the building of the neurological clinics of La Salpêtrière in 1964. Collection of the Department of Neuropathology Raymond Escourolle, Pitié-Salpêtrière Hospital.

Figure 10. Marble plaque in memory of Raymond Escourolle, first department head of the independent laboratory of neuropathology of La Salpêtrière :

«This Neuropathology Laboratory is dedicated to the memory of Raymond Escourolle, who founded it in 1964 and directed it until 1984. For his students, he remains its soul».

Raymond Escourolle Department of Neuropathology, Pitié-Salpêtrière Hospital. Collection of the Department of Neuropathology Raymond Escourolle, Pitié-Salpêtrière Hospital.

Girard

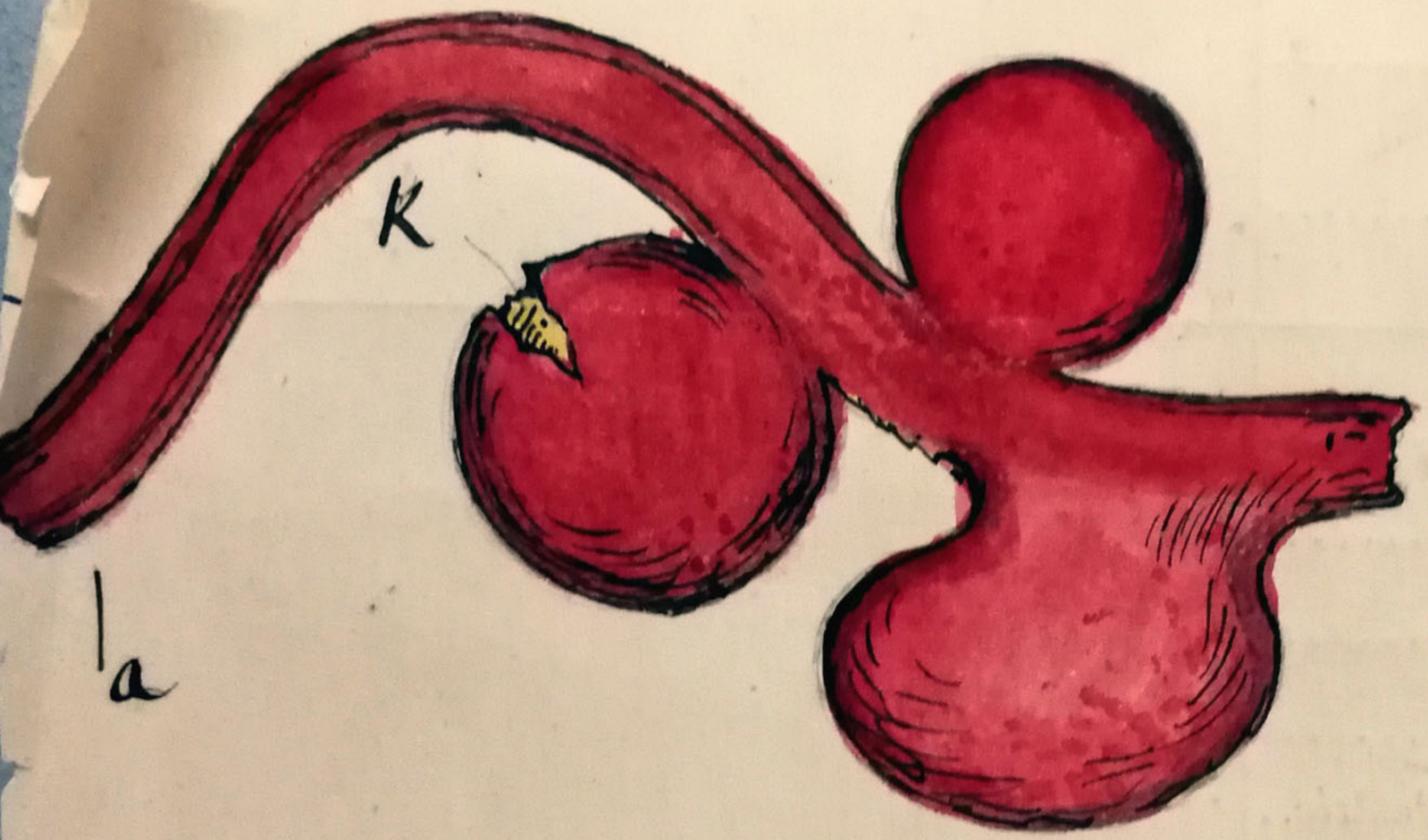
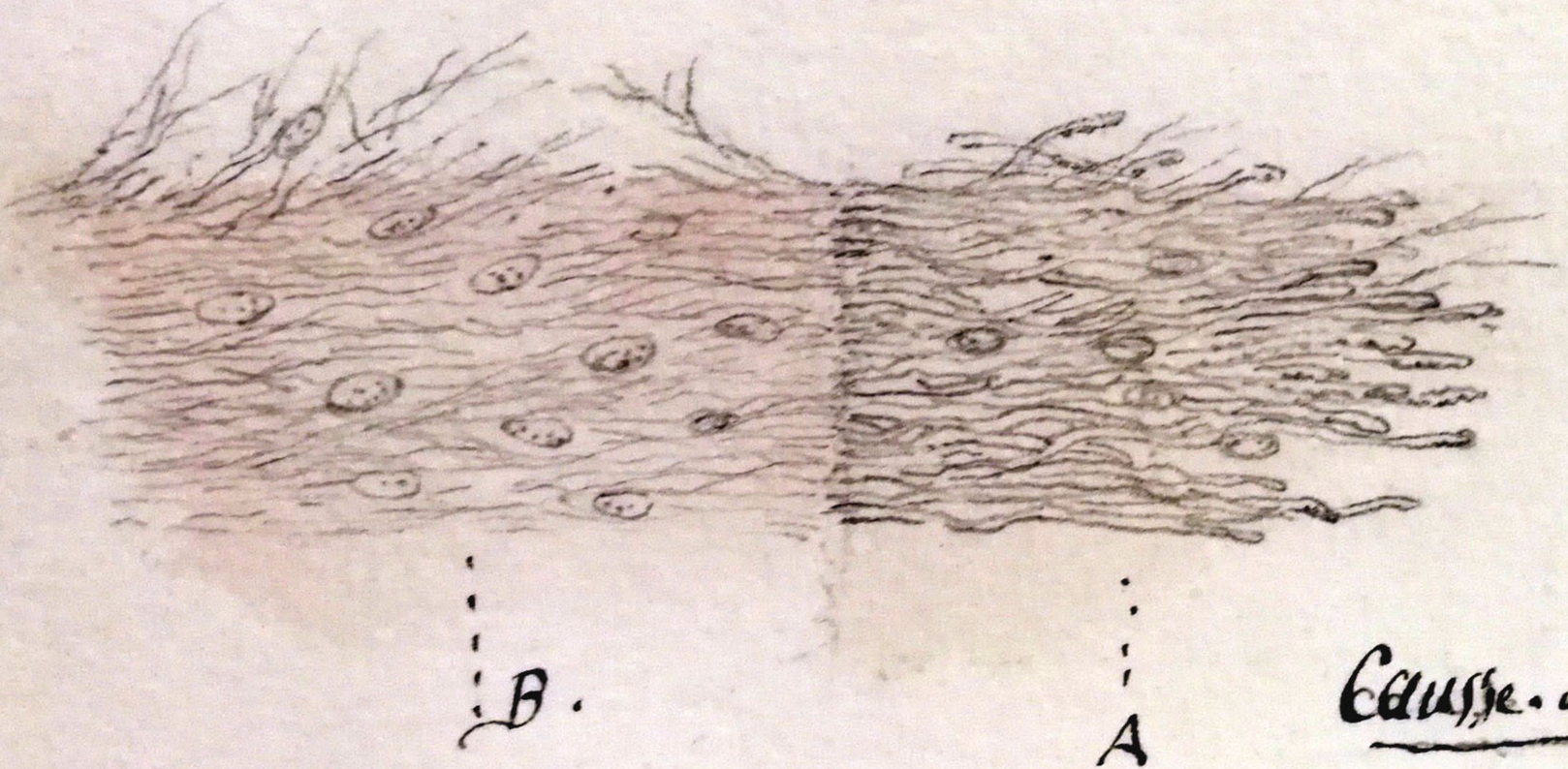


Fig 9

Siège à l'origine de la face externe des circonvolutions.

a. Le Vaisseau a $\frac{26}{100}$ $\left(\frac{1}{4}\right)$ de millim de diamètre
– Ce Vaisseau malgré son diamètre ne porte pas de fibres musculaires ; ses parois sont remarquables épaisses – et portent beaucoup de noyaux.

En K. déchirure de la paroi extérieure d'un anevrysme laissant voir les pes. sus jacentes, non colorées par le carmin.



A. pe. peripheriques.
la Ochas de la plaque

B. la plaque.

Eclusse. Protuberance

Acide Chromique.

a b c d.

a. bulbe
b. moelle cervicale
c moelle dorsale
d. moelle lombaire.

CHARCOT

A L'AMPHITHÉATRE DE LA SALPÊTRIÈRE

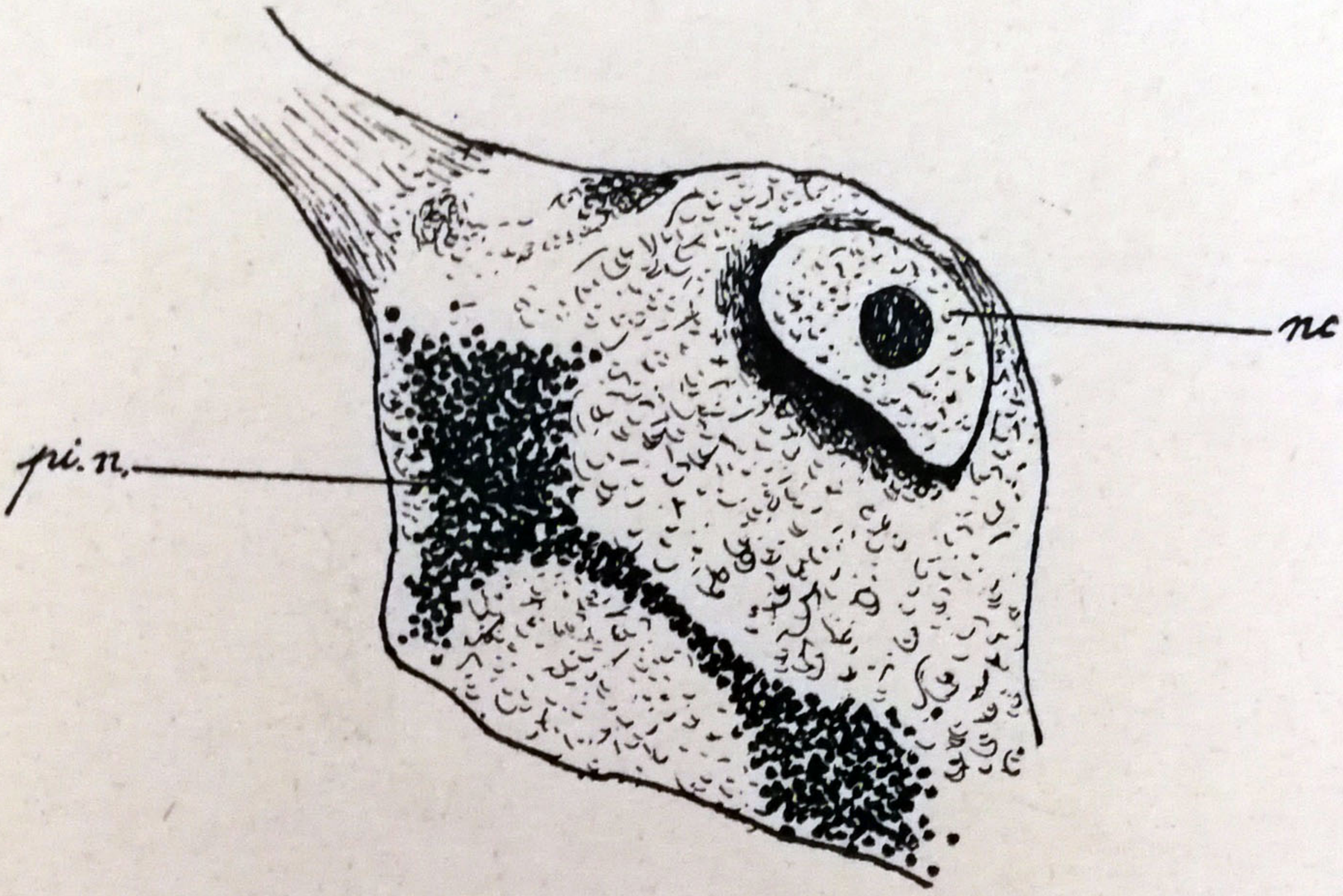


Fig. 11

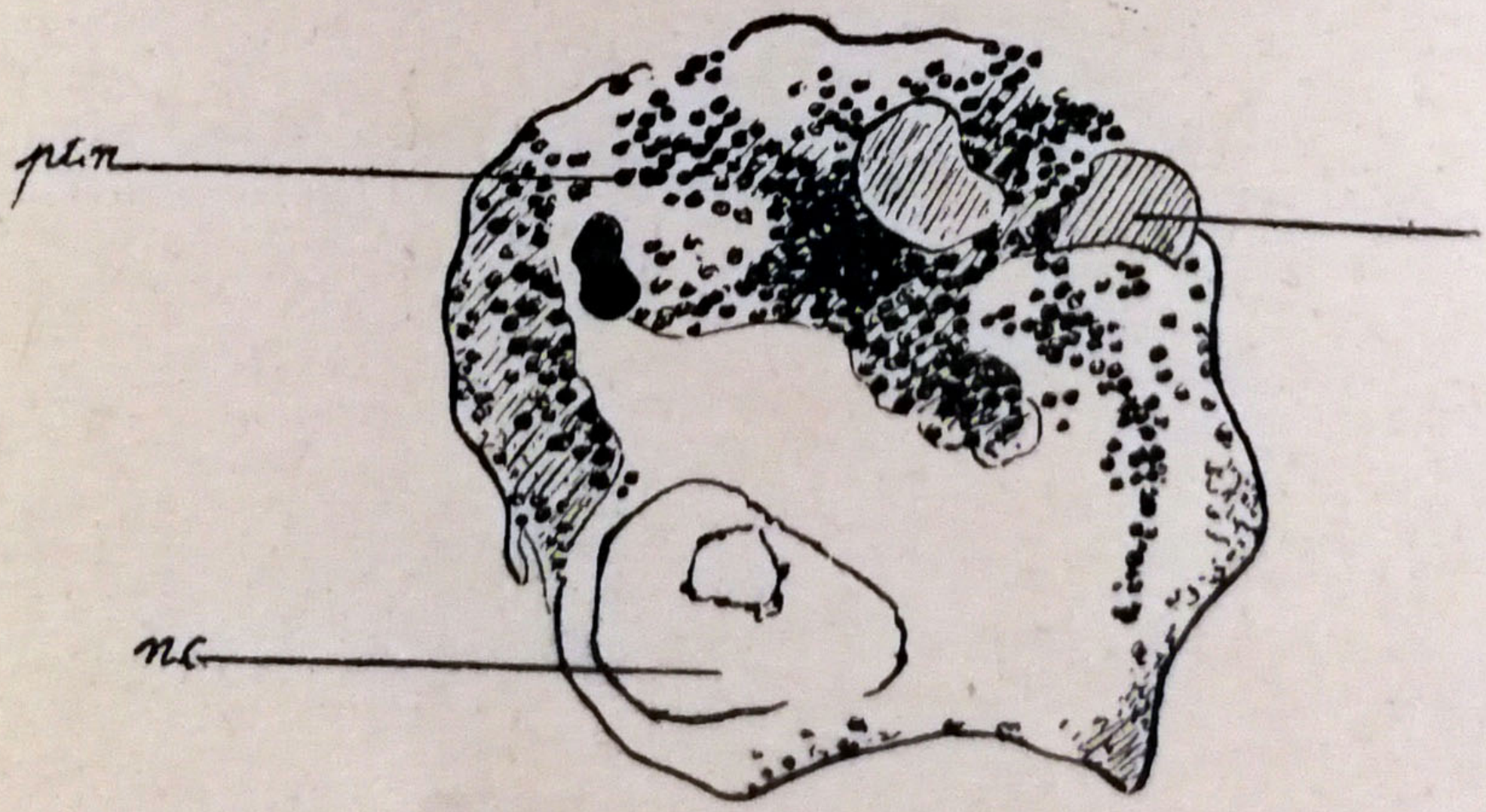


Fig. 9

Fig.1

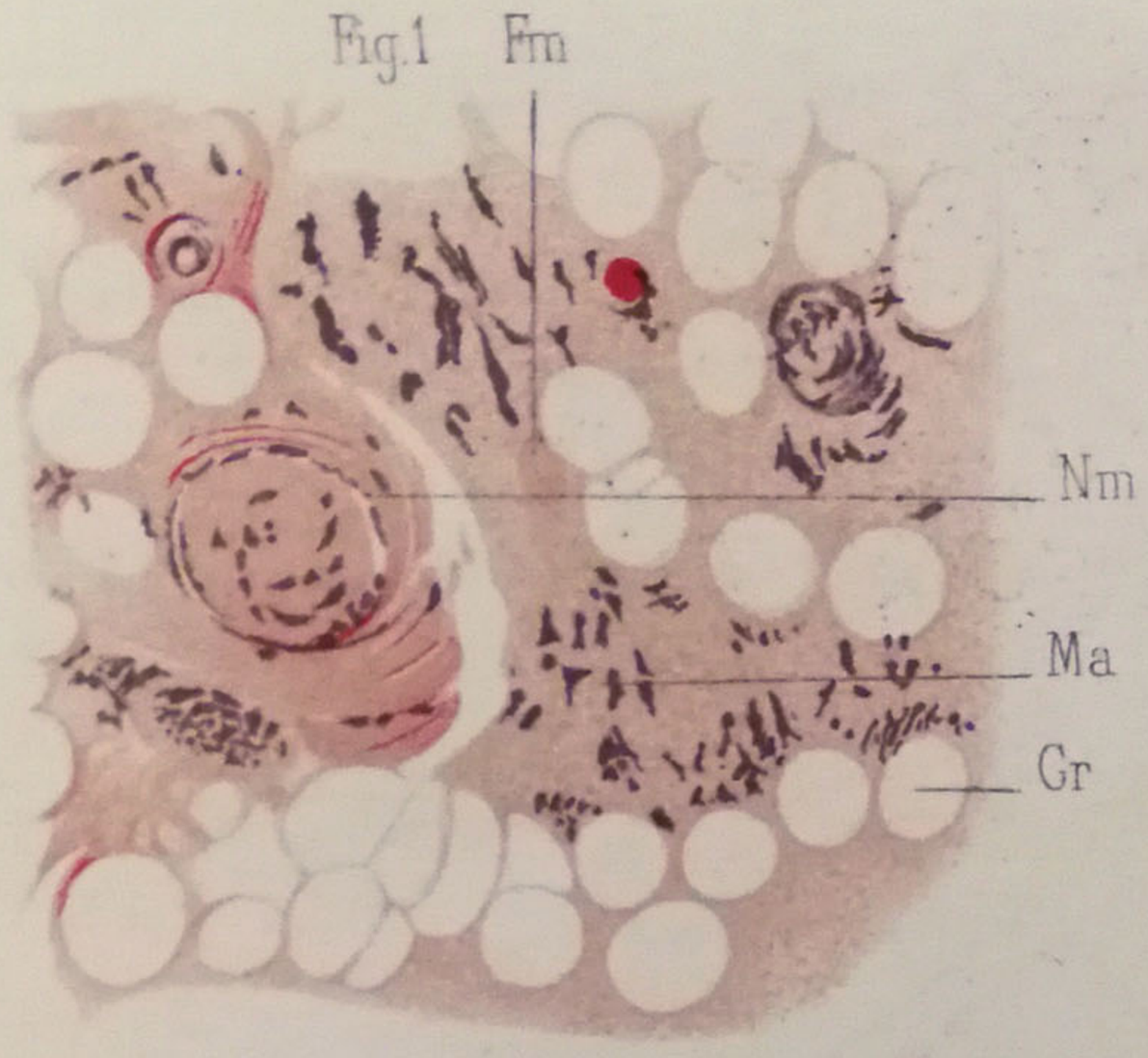
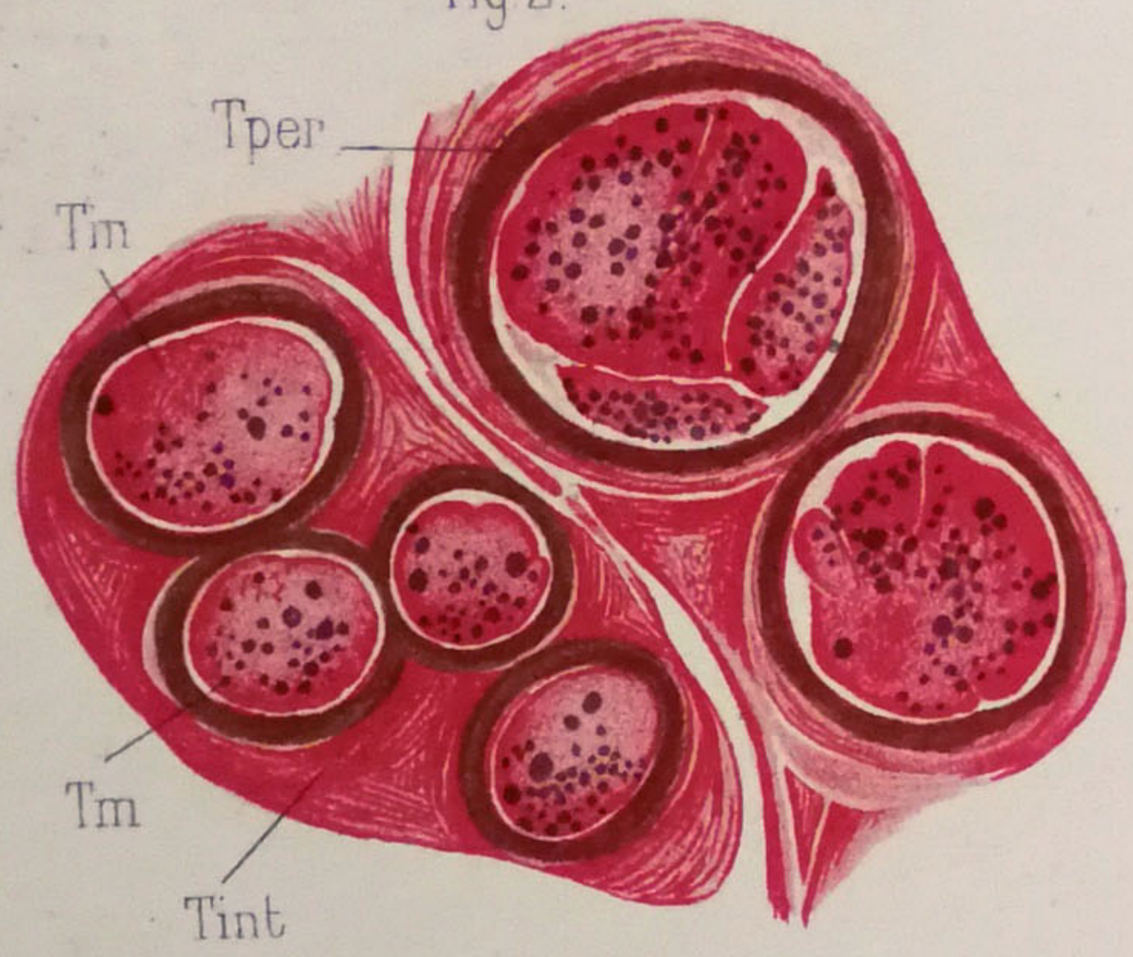


Fig 2.



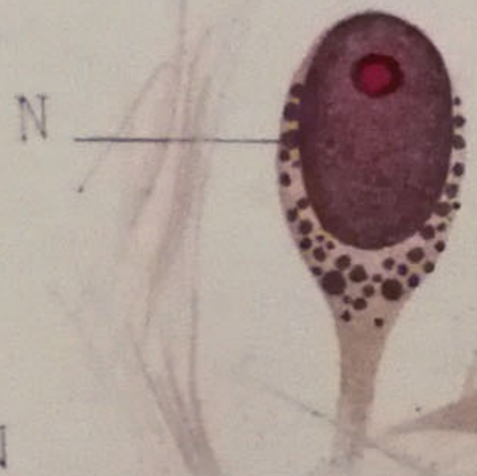


Fig.7.

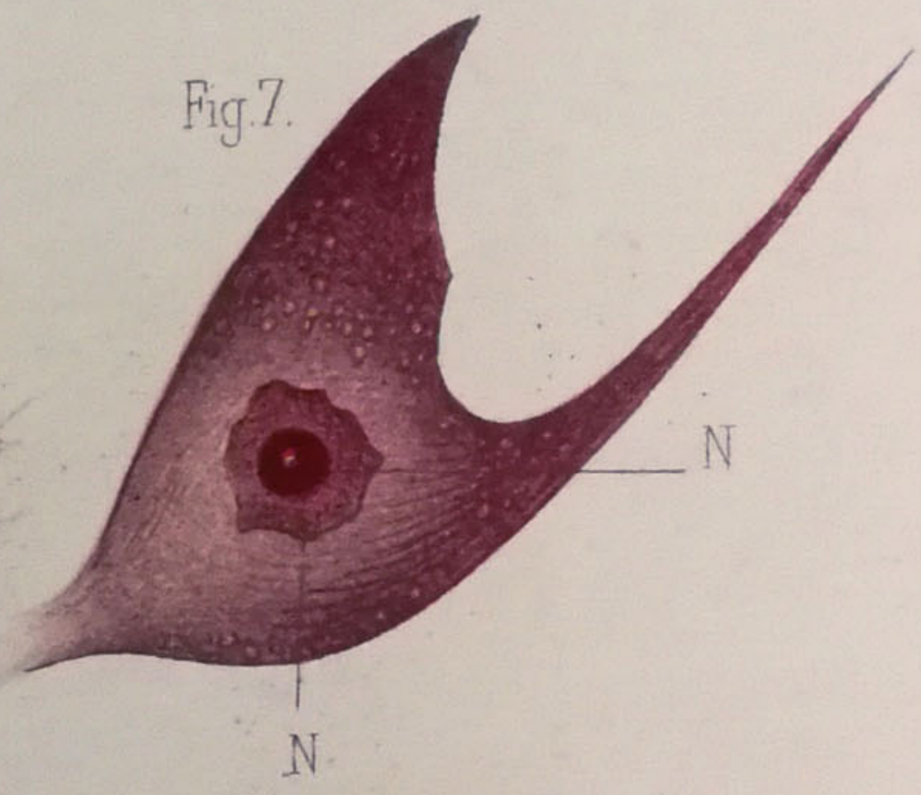
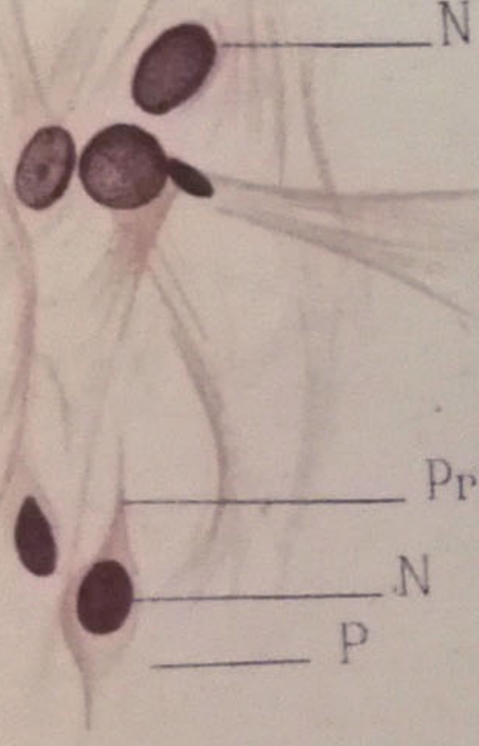
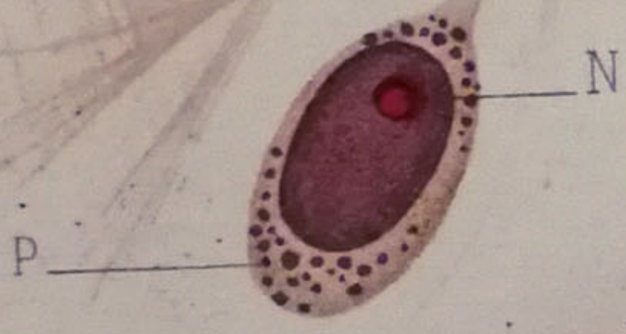


Fig 8.





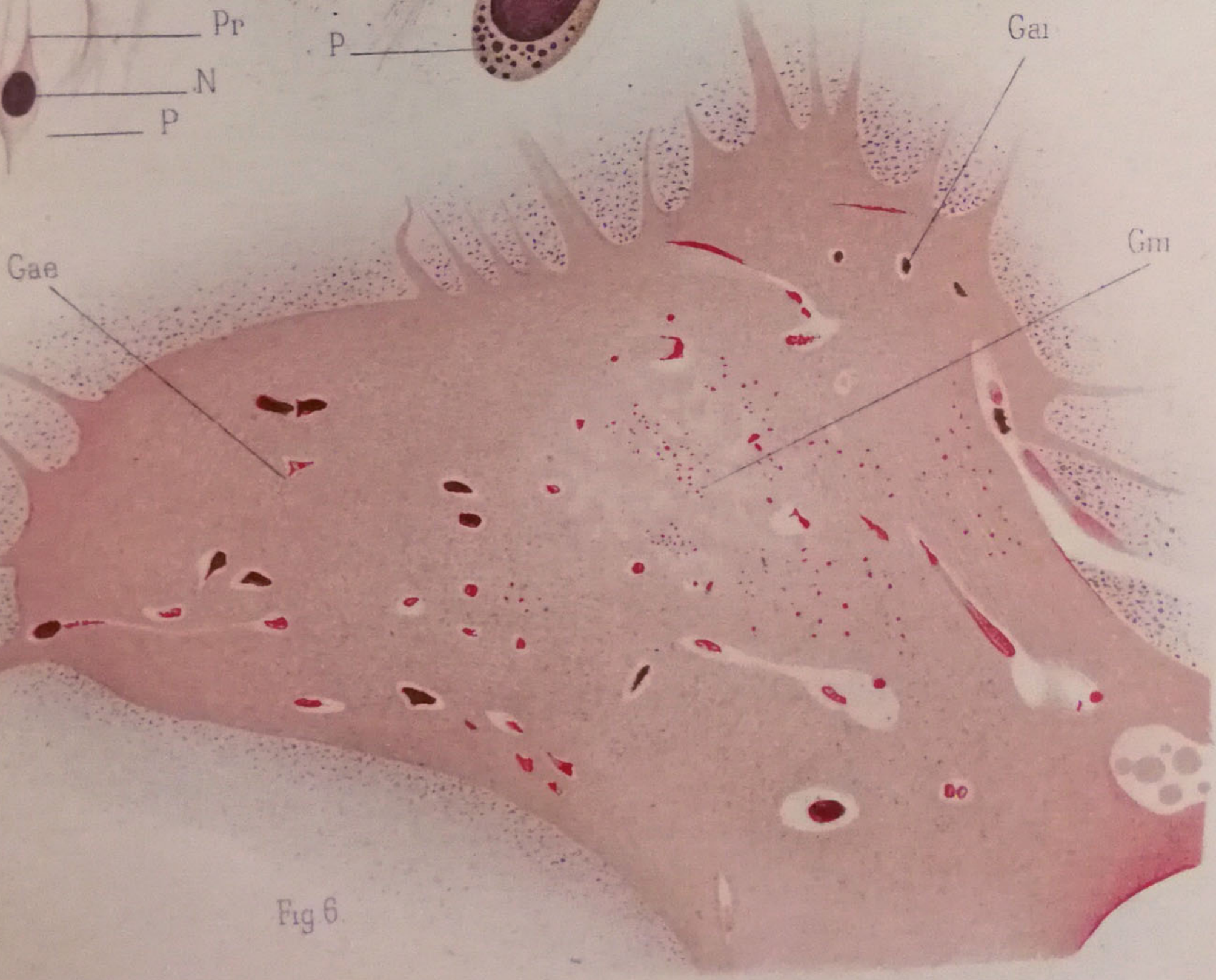


Fig 6.

Ce LABORATOIRE de NEUROPATHOLOGIE

est dédié à la mémoire de

Raymond ESCOUROLLE

qui l'a fondé en 1964

et l'a dirigé jusqu'en 1984.

Pour ses élèves, il en reste l'âme.