REVIEW

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Georges Marinesco (1863–1938): neurologist, neurohistologist and neuropathologist

M. CATALA[1)], J. POIRIER[2)]

[1)]*Professeur à l'Université Paris-VI (Pierre-et-Marie-Curie), Praticien Hospitalier au Groupe Hospitalier Pitié-Salpêtrière, Paris, France*

[2)]*Professeur honoraire à l'Université Paris-VI (Pierre-et-Marie-Curie), Ancien Chef de service au Groupe Hospitalier Pitié-Salpêtrière, Paris, France*

Abstract

Gheorghe Marinescu (Georges Marinesco, in French) is a Romanian physician, founder of the School of Neurology in that country. He begins his medical studies in Bucharest, then has the opportunity to reach Paris and join the School of Neurology in *La Salpêtrière* Hospital, lead by Jean-Martin Charcot. This trip will forever imprint the mind of Marinescu, a great friend of France, a respectful student of Charcot and a friendly colleague of many Parisian neurologists. Marinescu's works are multiple and very important. He describes the succulent hand in syringomyelia and the palmar-jaw reflex. Marinescu is also one of the first to use the cinema for medical purposes. His work as an anatomo-clinician, a method developed by Charcot, is important. We denote the description of the *locus niger* affected by tuberculosis in a case of parkinsonism (this description paving Etienne Brissaud's way to highlight the anatomical origin of Parkinson's disease), the original clinical description of Marinesco–Sjögren syndrome, and that of medullomyoblastoma. Marinescu is also a famous neurocytologist as evidenced by his work, *La Cellule Nerveuse*, published in 1909. The first volume of the book is devoted to the aspects of the normal nervous tissue: the neurofibrillar network, the chromatophilic elements, and the paranucleolar corpuscles (now known as Marinescu's bodies). The second volume of the book is almost related to features revealed by experimental lesions: chromatolysis and neuronophagia. Furthermore, Marinescu describes with Oscar Blocq, small nodules than are now regarded as the first description of senile plaques.

Keywords: Gheorghe Marinescu, history of neurosciences, medical cinematography, senile plaque, Parkinson's disease, chromatolysis, neuronophagia.

Famous Romanian physician and founder of Neurology in that country, Gheorghe Marinescu (Georges Marinesco, in French) (Figure 1) was born in Bucharest on February 23rd, 1863 and died on May 15th, 1938. He completes his training in France, with the greatest masters, including Pierre Marie (1853–1940), Fulgence Raymond (1844–1910), Joseph Babinski (1857–1932). But, above all, he is and introduces himself as a student of Jean-Martin Charcot (1825–1893).

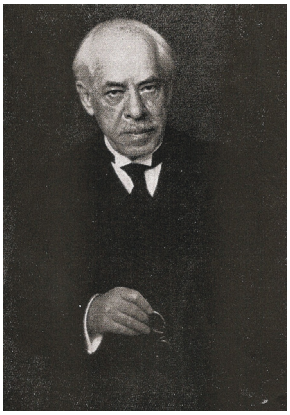


Figure 1 – ***Georges Marinesco. Volume jubilaire en l'honneur du professeur G. Marinesco, Institut d'Arts Graphiques E. Marvon, Bucarest, 1933 [49].***

Georges Marinesco studies medicine in the School of medicine of the Brancovan (Brâncoveanu) hospital in Bucharest and becomes the assistant (*préparateur*) of Victor Babès (1854–1926) in the Institute of Bacteriology. He graduates in 1889. Victor Babès gets him a scholarship from the Government that allows him to spend nine years in Paris studying Neurology. He joins at the *Clinique des Maladies du Système Nerveux* (Clinic for Diseases of the Nervous System) lead by Professor Jean-Martin Charcot in the Salpêtrière hospital. Throughout his life, he remains faithful to Charcot's memory, and he continues to present himself as his pupil and shows the admiration that he has for him. It is particularly meaningful that Marinesco is chosen to speak on behalf of the twenty-three delegations that come to represent the former students of the master during the festivities celebrating the 100th anniversary of his birth. Jean-Baptiste Charcot, son of Jean-Martin Charcot, will thank him by addressing these words: "*you are the grateful and affected student of the father, and the exquisite friend of the son*". The subsequent stays of Marinesco with the pathologist Carl Weigert (1845–1904) in Frankfurt and the physiologist Emil du Bois-Reymond (1818–1896) in Berlin leave a much lesser mark on him.

Thanks to *La Semaine Médicale* in 1896, he travels abroad to write reports on foreign schools of Neurology [1]. He meets the salient masters in this area: in England, John Hughlings Jackson (1835–1911), William Richard Gowers (1845–1915), David Ferrier (1843–1928), Sir William Henry Broadbent (1835–1907), Sir Victor Horsley (1857–1916), Sir Henry Head (1861–1940); in Germany, Wilhelm Erb (1840–1921), Eduard Hitzig (1838–1907), Karl Wernicke (1848–1905), Rudolph Albert Kölliker (1817–1905), Hermann Oppenheim (1858–1919), Wilhelm Waldeyer-Hartz (1834–1921); in Italy, Cesare Lombroso (1835–1909), Camillo Golgi

(1844–1926), Giovanni Mingazzini (1859–1929); in Spain, Santiago Ramón y Cajal (1852–1934); in Russia, Wladimir Bekhterev (1857–1927), Alexis Kojewnikow (1836–1902), Sergei Korsakow (1856–1900), Alexander Stanislavovich Dogiel (1852–1922); in Switzerland, Constantin Von Monakow (1853–1930), Auguste Forel (1848–1931); in Sweden, Gustaf Retzius (1842–1919), Alarik Frithiof Holmgren (1831–1897); in Belgium, Arthur Van Gehuchten (1861–1914). After all these contacts, Marinesco concludes: "*Well! None of these eminent masters played an influence as considerable as Charcot's on my mind and my research*" [2].

During the celebration of both the centenary of Charcot's birth and the XXVth birthday of the *Société de Neurologie de Paris* (Society of Neurology of Paris*)*, Marinesco multiplies his signs of reconnaissance and gratitude and insists on the direct filiation between the Romanian Neurology that he is creating and the French Neurology that taught everything to him [3]. Throughout his career, he keeps in touch with his Parisian colleagues in particular Charcot's students with whom he tied friendly relations during his stay in *La Salpêtrière*. His articles are drafted in French and published in French journals with only few exceptions. This Marinesco's francophilia is highlighted by his attitude during World War I. After the victory of Argesh that leads to the occupation of Bucharest by the armies of the Central Empires, the Romanian government takes refuge in Jassy (at present Iaşi). Georges Marinesco follows this retreat, but leaves the region to return to France after a stressful journey through Russia, Finland, Scandinavia and finally the UK. He spends the rest of the war in the region of Paris at Henri Meige's home (1866–1940) and worked at *La Salpêtrière* with Pierre Marie.

The work of Marinesco is considerable, both quantitatively and qualitatively. His prolixity is amazing, covering all areas of neurology, neurohistology and neuropathology "*more than 1,500 scientific work during 49 years of work*" [1]. Many of his articles are written in collaboration first with colleagues and/or friends of *La Salpêtrière*, as Paul Oscar Blocq (1860–1896) and Achille Souques (1860–1944), and after his return to Romania with his students. It is difficult to discern strong axes in his work, because everything that affects the nervous system either normal or pathological is addressed. That is it is out of the question to review exhaustively here all the subjects that he approaches. Ignoring numerous publications, we selected the most significant works, focusing on the histological, embryological and neuropathological domains.

Marinesco, neurologist

Upon his return to Bucharest, in 1897, Marinesco obtains the direction of a neurological department in Pantelimon then Colentina hospitals, and shortly after, he becomes the first Professor of the Chair of Neurology created for him at the Faculty of Bucharest. He assumes the position for forty-one years. Marinesco is thus recognized as the founder of Romanian Neurology.

Clinician and researcher, Marinesco is also a teacher of great talent. He teaches numerous students, many of whom became Professors of Neurology: Constantin Ion Parhon (1874–1969), founder of the Romanian School of Endocrinology, First President of the Presidium of the new *People's Republic of Romania* from 1948 to 1952, Moses H. Goldstein (1872–1975), Ion Minea (1878–1941), Nicolae Ionesco-Sisesti (1888–1954) Marinesco's successor to the Chair of Neurology in Bucharest, Anghel Radovici (1887–1957), State Draganesco (1891–1964), Oscar Sager (1894–1981) holder of the Chair of Neurology in Timisoara then successor of Ionesco-Sisesti for the Chair in Bucharest, Arthur Kreindler (1900–1988) Professor of Neurology at the Institute for the development and specialization of physicians, D. Grigoresco (?–?) and Jean Nicolesco (1885–1957), the best known Romanian Neurologist in France, thanks to the famous handbook he publishes in 1925 with Charles Foix (1882–1927) [4].

His work as neurological semeiologist is modest. Note the description of the "*main succulente*" (succulent hand) in syringomyelia, swelling of the dorsum of the hand in which the skin is "*lisse, luisante et unie*" (smooth, shiny and uniform) because of cutaneous vasomotor and trophic disorders associated with muscle atrophy [5] and of the palmar-jaw reflex [6]: a friction, moderately strong, of the thenar eminence from the base of the thumb to its tip triggers a contraction of the ipsilateral chin tuft. It is an archaic reflex, present in the very young child, disappearing when the brain is mature and reappearing in certain pathological circumstances. It is classically considered as the mark of a frontal lesion, but it has actually no localizing value [7] and can be observed both in normal subjects and patients with neurological diseases [8, 9].

In his monograph on muscle tone [10], foreword by Sir Charles Sherrington (1857–1952), neuromuscular exploration by studying the chronaxia and rheobase [11] plays an important role. These techniques are now abandoned since they are of no use in light of the current possibilities of exploration [12].

The admiration of Marinesco for Pavlov has no limit. He concludes his book [13] devoted to conditional reflexes and dedicated "*To the great physiologist I.P. Pavlov*" with these words: "*The doctrine of conditional reflexes, as was inaugurated by Pavlov, Bekhterev and their students, not only casts a bright light on the physiological processes that occur in the cerebral cortex, but psychology, psychiatry and nervous pathology have largely benefited from these discoveries. We believe that this is only the beginning*".

In his many articles on hysteria [see in particular 14–16], he pays tribute to Babinski, but believes that conditional reflexes have an important role: "*The problem of hysteria is not yet solved and the theory of pithiatism does not represent the final stage in the evolution of our knowledge.*" [17].

Finally, Marinesco is a pioneer in the development of medical cinematography [18]. Marinesco's stay in Paris is fruitful in this area since he meets with physiologist Etienne Jules Marey (1830–1904) who has largely used the invention of the Lumière Brothers. Between 1898 and 1901, Marinesco, aided by two

assistants (Parhon and Goldstein), produces several films showing clinical signs presented by patients with neurological diseases. Unfortunately, most of these films have been lost forever. Only a few copies have been restored and presented for the first time in 1973 during the Franco-Romanian Seminar. Two of these films, walking troubles in organic hemiplegia (1899) and a case of hysteric hemiplegia cured through hypnotic suggestion (1899), can be found on http://www.dailymotion.com/video/x5nzx1_studies-on-human-pathological-locom_short films or http://www.veengle.com/s/Films%20médicaux.html. Auguste Lumière, himself, congratulates Marinesco for using the cinematograph to study medical cases (1924): "*I have seen your scientific reports about the utilization of the cinematograph in studies of nervous illnesses, when I was still receiving* La Semaine Médicale*, but back then I had other concerns, which left me no sparse time to begin biological studies. I must say I forgot those works and I am thankful to you that you reminded them to me. Unfortunately, few scientists have followed your way*."

Marinesco, anatomo-clinician

As a true pupil of Charcot, Marinesco is an enthusiastic follower of the anatomo-clinical method that he illustrates with numerous publications of which we will retain here four particularly instructive examples.

With Paul Oscar Blocq (1860–1896), Charcot's *interne* in 1887, Marinesco describes in 1893 a case of parkinsonism due to a tumor of the *Substantia Nigra* (*locus niger*) [19]. In 1894–1895, Édouard Brissaud (1852–1909), revisiting this observation of Blocq and Marinesco, notes that the tuberculous tumor reported by these authors completely destroys the *locus niger* and causes a Parkinsonian hemiplegia on the opposite side of the lesion. While the dominant etiological conceptions at that time implicate a neurosis or muscle or cortical pathology, Brissaud from this observation, suggests that a "*lesion of the locus niger could be the anatomical substratum of Parkinson's disease.*" [20]. Although the brilliant idea of Brissaud has not been seriously considered by his colleagues, the future has confirmed his prescient intuition: in 1919, Constantin Trétiakoff (1892–1956), while histologically studying the *locus niger* of nine Parkinsonian patients, demonstrates that the lesion responsible for the disease is a depigmentation of the neurons of the *locus niger*.

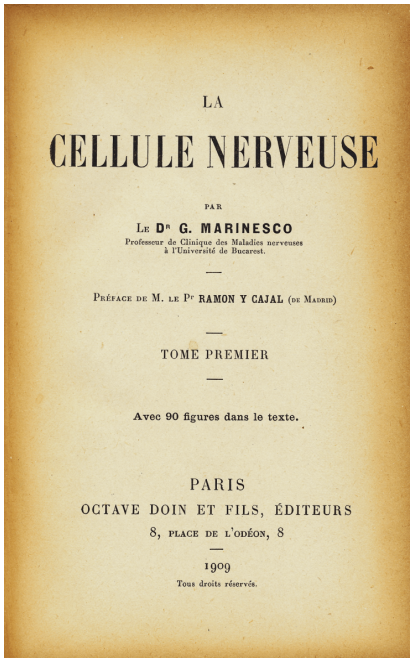
About an anatomo-clinical case report of an atonic-astasic syndrome described in 1909 in childhood by Otfrid Foerster [21], Marinesco [22] notices that the clinical syndrome is well known (hypotonia, affecting mainly the lower limbs, hypertonia in the vertical position, mental disorders, speech disorders, abnormal movements). However, he states that its anatomico-pathological substratum is ill defined and even not identical in all cases.

The so-called Marinesco–Sjögren syndrome, first described by Marinesco in 1931 [23] and by the Swedish doctor Karl Gustaf Torsten Sjögren (1896–1974) in 1950 [24, 25], is characterized by ataxia due to cerebellar atrophy, congenital cataract and severe mental retardation. Other signs are frequently encountered such as dysarthria, nystagmus, hypotonia and muscle weakness, small stature and various bone abnormalities. Despite the severity of disability, patients bearing this syndrome have a life expectancy close to normal. We now know that this syndrome belongs to the group of autosomal recessive cerebellar ataxias, implicating chromosomes 18qter and 5q31. Marinesco–Sjögren syndrome with peripheral neuropathy and myoglobinuria and CCFDN syndrome (Congenital Cataracts Facial Dysmorphism Neuropathy) are genetically identical and are caused by a mutation of the *SIL1* gene [26].

Marinesco describes a new variety of cerebellar medulloblastoma, containing striated muscle fibers, the medullomyoblastoma [27].

Marinesco neurohistologist

Unlike Charcot and most of his students, Marinesco, much more like Alfred Vulpian (1826–1887), Louis Ranvier (1835–1822) and especially his Hispanic mentor Santiago Ramón y Cajal, is an experimenter, as evidenced for example by much of his works on the degeneration and regeneration of the nervous centers and the peripheral nerves, or by the discovery of the fibers connecting the frontal lobe with the striatum after partial or complete destruction of the frontal lobe in the ape and the dog [28]. But, he is primarily a neurocytologist has written multiple publications [referenced in 29] on the biology and fine structure of the nerve cell and its organelles (Nissl bodies, neurofibrils, pigments, nucleus and nucleolus) in normal state and in pathology. These works are largely described in his 1909 book (Figure 2), but they are not interrupted at that time and continue until his death.


LA

CELLULE NERVEUSE

PAR

LE Dr G. MARINESCO

Professeur de Clinique des Maladies nerveuses à l'Université de Bucarest.

—

PRÉFACE DE M. LE Pr RAMON Y CAJAL (DE MADRID)

—

TOME PREMIER

—

Avec 90 figures dans le texte.

PARIS

OCTAVE DOIN ET FILS, ÉDITEURS

8, PLACE DE L'ODÉON, 8

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1909

Tous droits réservés.

Figure 2 – ***Flyleaf of "La Cellule Nerveuse" published by G. Marinesco in 1909 [29].***

Santiago Ramón y Cajal, to whom his book on the nerve cell [29] is dedicated, writes a laudatory preface, in which he emphasizes that his "*honorable colleague*

and learned friend Professor Marinesco" is "*all at once a shrewd observer and a strong and tenacious supporter of the experimental method*" and that "*his indefatigable activity, his fruitful research in the so difficult field of nervous system histology have earned him a reputation and more than enough authority to impose his own book to the attention and praise of the learned world*."

In fact, this monumental two-volume work is a general very complete and abundantly illustrated review, showing all the literature of the time, and in which Marinesco incorporates, as appropriate, the results of his own research. The first volume is devoted to cytology, embryology and the physiology of the nerve cell and the second to pathology. His research incidentally focuses on the relations of contiguity and not continuity between nerve cells, as it unambiguously follows Ramón y Cajal adopting unreservedly the neuronal theory. Marinesco almost solely focuses on the cytology of the nerve cell under physiological conditions and in various pathological and/or experimental conditions.

In the first volume, the general morphology of the neuron, its volume and fine structure are successively considered. All components that are known at the time by optical microscopy and techniques of fixation and staining recently developed, are reviewed in details: nucleus, chromatophilic elements (corpuscles of Nissl), neurofibrils, internal reticular apparatus of Golgi, bioblasts of Altmann (mitochondria), centrosome, coloured granules (the black pigment of both *locus niger* and *locus coeruleus* and the yellow pigment).

For Marinesco, the fibrillar structure of the achromatic figured substance – future neurofibrils – is obvious, "*it is a given feature now belonging to science*" [30, p. 5]. These fibrils form a network inserted at the cell periphery and at the wall of the nucleus in the centre. Thus, he calls this structure *spongioplasma*. He shows that the fibrils of the dendrite and axon are in direct anatomical continuity with the intracytoplasmic network lying in the cell body. He is the first to conclude that this continuity explains the fact that lesions of the spongioplasma cause degeneration of peripheral extensions of the nerve cell [30, p. 9] and he deduces, as Cajal and Van Gehuchten that "*the organized achromatic substance as well as fibrils of the cylindraxis are used to assure conduction of nerve impulses*." [30, p.11], but also that there is "*something in the achromatic substance that maintains or rather regulates nutrition of the cylindraxis and it is for this reason that I gave the achromatic substance the name* trophoplasma*, that is to say, the plasma which governs the nutrition of the neuron*." [30, p. 14].

Regarding the role of the chromatophilic elements, Marinesco does not side with Van Gehuchten who admits that "*the chromatic substance is a reserve of nutrients, a sort of nutritive attic*." [30, p. 11]. He thinks that the small chromatophilic items (which after Cajal are continuous with the fibrillar network) also conducts the nervous impulses – not that his opinion is decisive about it – the big chromatophilic elements influence "*the intensity of the nervous impulse*" through "*the chemical changes that the impulse generates in the chromatophilic elements*". "*Chromatophilic elements should not be regarded as nutrient reserves, but as a functional substance, enjoying considerable chemical properties giving rise, because of their wear and tear, to a certain amount of mechanical energy*." "*The chromatophilic elements represent a substance with high chemical potentials, which is the seat of continuous phenomena of integration and disintegration, and it is through these phenomena that the nerve cell becomes a energetic device.*" This accounts for the name he gives to them: kinetoplasma [30, p. 13]. Thus, for him, "*chromatophilic elements are the seat of intense chemical phenomena and, therefore, we considered cell activity as a chemical process. The nature of this process would be difficult to define*." [30, p. 13]. But, since function and nutrition are two related phenomena, he does not deny the important role that these elements play in the nutrition of the cell.

"*The nucleus of the nerve cell also undergoes the shock wave that propagates inside the cell, this shock leaves a fixed residue in the nucleus; this residue is somehow the anatomical basis for various psychological processes*." [30, p. 11–12].

About *paranucleolar corpuscles*, small acidophilic inclusions, forming droplets, present in the nucleus of pigmented neurons in the *substantia nigra* and *locus coeruleus*, which he described in humans [31], he notes that these inclusions (later named Marinesco bodies) are more abundant in adults and the elderly than in the young and they are absent in children. Their histological characteristics are further detailed in his 1909 book on the nerve cell [29]. Some later works have attempted to define the meaning of Marinesco bodies. An age-related cell involution without pathological significance [32, 33] or, conversely, a pathological process such as Lewy body disease [34] and myotonic dystrophy [35] have been advocated (Figure 2).

Unconditional follower of the neuronal theory defended by Cajal, it does not subscribe to destabilization attempts by several authors in the early XXth century. For example, he refutes "*in situ autonomous regeneration of a nerve fragment separated from its centre by nerve section*" [36]. He states: "*The neuron lives only through its functions. Thus, a nerve centre, separated from the extremity that sends it excitations or the one it sends itself functional stimulations, can not live indefinitely, it atrophies*." [29, vol. II, p. 197]. Marinesco devotes a chapter to the *theory of dynamic polarization* proposed by Cajal – the nerve impulse travels from the periphery to the cell body in dendrites and vice-versa in the cylindraxis – and another to the *theory of amiboism and neuronal plasticity*. This theory, scaffolded by Lépine and Mathias Duval (1844–1907), is based on the idea that for all the nerve cells, the terminal branches of axons are endowed with amoeboid movements that may cause in certain circumstances the retraction of the cell – and thus a relaxation of contiguity of neurons and

suspension of brain activity, reflecting some sleep and anesthesia or hysterical paralysis – or, rather, its expansion – and thus a more intimate contact between neurons accounting for activation of imagination, memory, or association of ideas.

Marinesco's contribution to neuro-embryology is quite limited although Chapter VIII of the first volume of *The Nerve Cell* is devoted to it [29]. This chapter is a general review, sometimes quite critical, of the data known at the time. Marinesco adds some personal experiences that do not diverge from the vision of his two mentors: Wilhelm His (1863–1934) and Santiago Ramón y Cajal. Thus, it adheres to the theory of the existence of two types of cells in the neural tube or neuroepithelium: germ cells (round cells near the ventricular region) that he considers as neuronal precursors and epithelial cells that generate the glial support. This concept is now largely obsolete, but at the time, no technique could confirm or deny these results. Unlike some authors of the Italian school, it also affirms the strict unicellular origin of each nerve process. In addition, he agrees with the opinion of Cajal on the existence of a chemotactic sensitivity of neurons explaining axonal growth. This assertion is awfully modern and the discovery of molecules which attract or repulse the growth cone definitely demonstrates this theory. Marinesco erroneously states that dendrites are formed passively because of the cell junctions of the membrane and active movements of the neuronal cell bodies. His histological studies of chick and mouse embryos (Figure 3), although incomplete, allow him to follow the theories put forward by His, Retzius and Lenhossek, Harrison and Cajal. It is important to note that Marinesco has access to human fetuses. He does indicate that the material is not exhaustive. However, obtaining such tissues is remarkable when you consider that at the time only those provided by spontaneous abortion could be used. Marinesco notes that all neurons are not born at the same time, a phenomenon now known as the temporal gradient of differentiation.

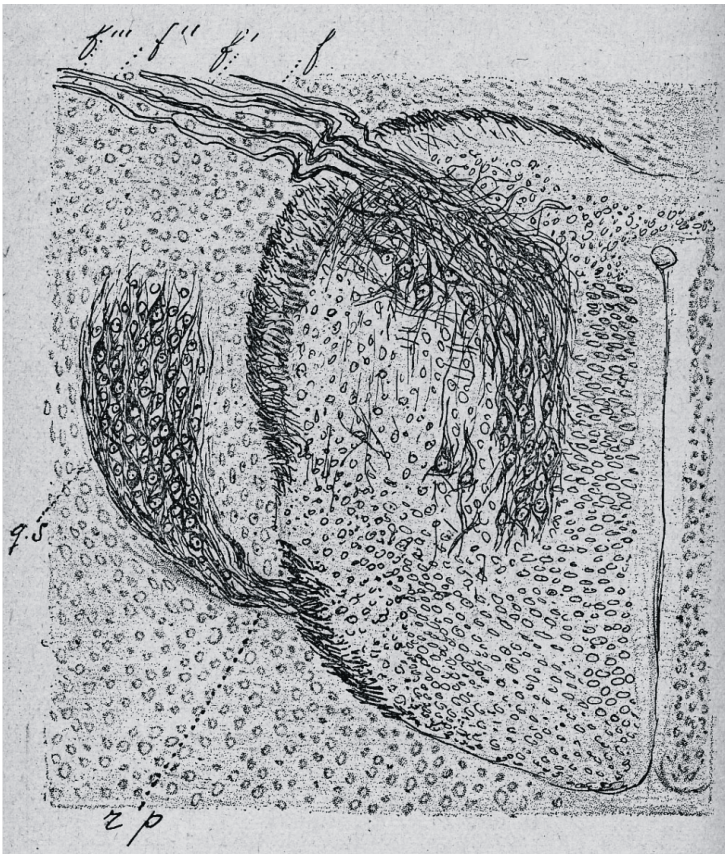

Figure 3 – ***Reproduction of Figure 76 (p. 356) from the first volume of "La Cellule Nerveuse" (G. Marinesco, 1909 [29]). This figure represents a transversal section of a histological preparation showing the nervous fibrils. This is from a chick embryo at six days of incubation. Ventral region is upside. "f" is for ventral roots, "gs" for spinal ganglion, and "rp" for dorsal roots.***

Marinesco, neuropathologist

At the beginning of his career in 1892, Marinesco collaborates on the atlas of histopathology of the nervous system edited by Paul Victor Babès and Oscar Blocq, by ensuring the fifth issue devoted to lesions of the posterior columns of the spinal cord [37]. Pierre Marie writes a laudatory comment in *La Revue Neurologique* [38]. During his stay in the neurological department of Charcot, he is the first with Blocq to describe, based upon the histological examination of brains removed from nine epileptic patients during autopsy, "*small nodules*" which will be later named senile plaques. He describes, in one case, "*scattered throughout the various layers of the cortex, small round clusters with a diameter of about 60 μm, distinguished from the rest of the tissue by a much more intense staining, and regular contours. They thus appear as vaguely dotted structures sprinkling the background of the slices. This is why it is possible to consider some of them at least as true multiple glial nodules* (?)." He connects them neither to senescence nor to a dementia syndrome [39]. Subsequently, he details the clinical and anatomical study of senile plaques [40, 41] (Figure 4).

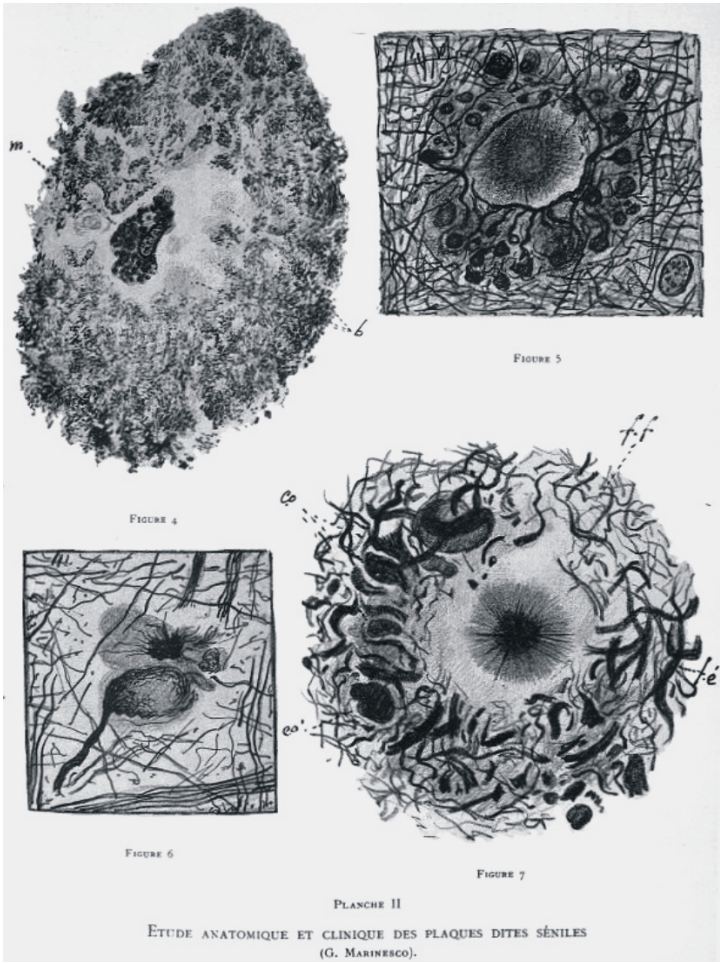

Figure 4 – ***Anatomical and clinical study of the so-called senile plaques, Marinesco G. (1912), Encéphale (Paris), 1er semestre, p. 105–132 [40]. Reproduction of the plate II. Fig. 4: Plaque with a large zonal layer constituted by an aggregation of filamentous material. A macrophage (m) lies in the center of the plaque and near the colorless and amorphous region. Fig. 5 shows a plaque with a bulky central nucleus and typical phenomena of neurotisation. The fibers coming from the new formation penetrate into the plaque. They arrive at the vicinity of the nucleus, they surround it and give off collaterals that end each with a button and form a rosette. Fig. 6. Fiber with a terminal ball. The black precipitate could be evidenced near it. The ball is degenerating. Fig. 7. Plaque with a central nucleus constituted by an argyrophilic central zone and a radial peripheral zone. The zonal layer is made up by fibers that are short, thick, sometimes thin at their extremity, undulated; by other thinner fibers (f, f) that creep into the first ones (f, e) forming ribbons and argentophilic corpuscles (ca, ca') around the central nucleus.***

In 1914 [42], he confirms the discovery in 1913 by Hideyo Noguchi (1876–1928) and Joseph Waldron Moore (1879–?) of the treponema invading the brain of patients suffering from general paralysis [43].

His major contribution to the histopathology of the nervous system is exposed in his report to Congress in Moscow in 1897 [30] and his work on the nerve cell [29], the second volume of which is entirely devoted to it. The strong points of these works concern the rigorous description of the two pathological phenomena which he names: chromatolysis and neuronophagia.

"*The term chromatolysis I applied to the processes of chromatophilic decay was adopted by most authors. As for the mechanism of this phenomenon, we find the period of assumptions. However, it is possible that there are several mechanisms that determine chromatolysis*." [28, vol. 2, p. 1]. Marinesco distinguishes *central chromatolysis* (Figures 5 and 6), which occurs in the cell body of the neuron after section of the axon or is the result of alterations in peripheral nerves [44], and *peripheral chromatolysis* that can be observed in primary lesions of the nerve cell, injured by traumatic, thermal or toxic causes.

Secondary cell damages determined by the nerve section (experimental study in rabbits) go through three phases: (1) a first stage reaction manifested by the gradual disappearance of chromatophilic elements lying in the centre of the cell body of the neuron with repulsion of the nucleus to the periphery (early perinuclear central chromatolysis), (2) followed by a phase of degeneration, which can lead to atrophy and disappearance of the cell, (3) but which is often replaced by a repair phase: neoformation of chromatophilic elements (the inverse of chromatolysis), the nucleus returns to a central position, the cell volume increases (hypertrophy) and then returns to normal.

In experimental lesions produced by trauma of the nerve centers in twenty young animals (rabbits, guinea pigs, cats, frogs) Marinesco finds, after initial necrosis, that cells and nerve fibers do not regenerate whereas glia and blood vessels proliferate. In primary lesions of the nerve centers observed in experimental anemia, rabies, botulism and tetanus, the lesions are highly variable. The chromatolysis may be most frequently peripheral (the disintegration of the chromatophilic elements beginning and predominating at the periphery of the neuronal cell bodies), sometimes perinuclear or diffuse, partial or general; phagocytosis by neuronophagia of degenerating nerve cells is then observed.

Neuronophagia, a term created by Marinesco, refers to the phenomenon of destruction of nerve cells by phagocytosis. Marinesco shows that phagocytes are not the glia cells – which proliferate when neurons are damaged – but Nissl mesh cells, that is to say motile cells derived from mesoderm, located near the neuron or migrated from blood vessels, and later assimilated by Marinesco to microglia [45].

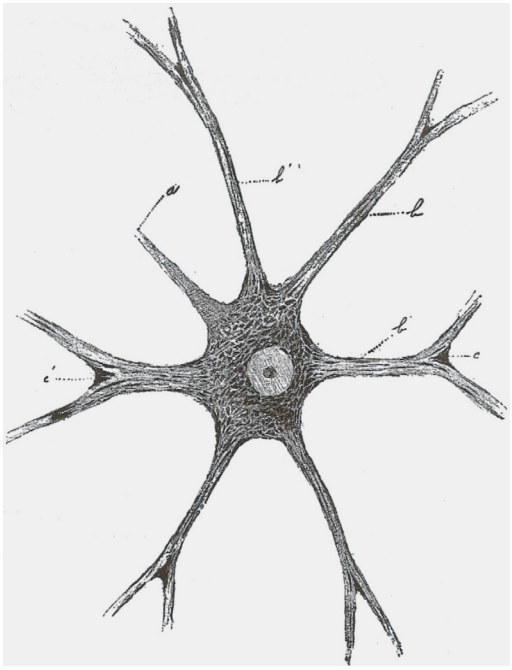

Figure 5 – ***Cell of the anterior horn in humans, Nissl staining. G. Marinesco, Des polynévrites en rapport avec les lésions secondaires et les lésions primitives des cellules nerveuses, Rev Neurol, 1896, 4^{e} année, n° 5 (15 mars), fig. 13 [44].***

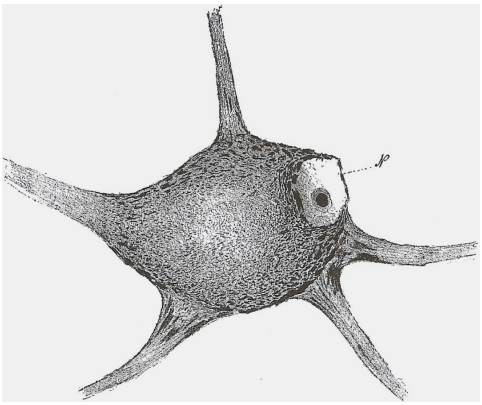

Figure 6 – ***Central chromatolysis. Cell of the anterior horn in a case of polyneuritis. Lesions are identical to those observed after a nerve section. G. Marinesco, Des polynévrites en rapport avec les lésions secondaires et les lésions primitives des cellules nerveuses, Rev Neurol, 1896, 4^{e} année, n° 5 (15 mars), fig. 17 [45].***

The image of Marinesco

Arthur Van Gehuchten (1861–1914), a neurologist and renowned neuroanatomist, professor at the Faculty of Medicine of the Catholic University of Louvain, frequently quotes Marinesco's works [46, 47].

In the French edition of his *Histologie du Système Nerveux*, published the same year as *La Cellule Nerveuse* by Marinesco, Ramón y Cajal [48] mentions several times the works of Marinesco including those relating to stainable granules of the nerve cells and the nucleolus. About chromatophilic clusters, he exposes and discusses Marinesco's theory and, without being able to prove it, he does not deny. He abundantly refers the works of Marinesco on chromatolysis and the changes involving the neurofibrillary reticulum under the influence of various pathological causes. However, in the general bibliography [48, vol. I, pp. 48–50], he mentions none of Marinesco's works.

The biggest names in European Neurology are involved in writing the *Jubilee Volume* published in his honor in 1933. Santiago Ramón y Cajal "*cordially*" congratulates "*the famous Romanian investigator*" and states that "*his work has been fruitful and multiple*." [49]. Jean-Alexandre Barré (1880–1967), Professor of Clinical Neurology in Strasbourg, ends his contribution by sending to Marinesco "*the homage of our admiration for the magnificent effort he continues to pursue in all areas of neurology, the high originality of his conceptions and the proven value of the knowledge that we owe*." [50]. In his opening remarks [51] of the XVIIth International Neurological Meeting, George Bourguignon (1876–1963), President of the Society of Neurology of Paris, pays tribute to Marinesco whose death has just been announced. He praises his merits both as the scientist and the great friend of France. Marinesco is a member of the Royal College of Physicians of London and corresponding member of the Academy of Medicine where his eulogy is pronounced by Louis Ribadeau Dumas (1876–1951) [52].

However, the glory of Georges Marinesco primarily stays in Romania: streets, boulevards, statues, museums, stamps (Figure 7), symposia, celebrations and commemorations abound in his homeland.

Figure 7 – ***Marinesco on a stamp edited by the Republica Populara Romina in 1963 at the occasion of the centenary of his birth.***

In 1963, the centenary of his birth gives rise to the publication of numerous articles in medical journals, mostly European (Romanian, Russian, Hungarian, Czech, German and French), but also in some Anglo-American ones and two volumes of selected works [53] for which his pupil Arthur Kreindler provides a long introduction [53, p. VII–XX] in which he paints a flattering portrait of Marinesco, insisting repeatedly on his materialism, on his interest in the defense of peasants, the working poor and the working class, as well as his relations with Soviet scientists and his admiration for Pavlov's conditioned reflexes [54].

Finally, what is the legacy today of the works of Georges Marinesco? His name is attached to the succulent hand in syringomyelia, the palmar-jaw reflex, the Marinesco–Sjögren syndrome, the princeps article of description of lesions of the *locus niger* in Parkinson's disease and, above all else, his work on nerve cell neurocytology and neuropathology, including

his rigorous and precise works on chromatolysis and neuronophagia that are still relevant today. According to the successful formula of the Canadian anatomist Murray Llewellyn Barr (1908–1995): "*La Cellule Nerveuse, together with Cajal's better known Histologie du Système Nerveux de l'Homme et des Vertébrés, are major chapters in the neurocytologist's Old Testament*." [55].

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Corresponding author
Martin Catala, Professor, MD, PhD, Department of Neurology (Pr Lubetzki), Groupe Hospitalier Pitié-Salpêtrière, 47–83 Bd de l'Hôpital, 75651 Paris Cedex 13, France; Phone (33–1) 44 27 36 90, e-mail: mcatala@snv.jussieu.fr

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