Antoni Grinyó Garriga (1903-1970), a Catalan neuroscientist who took exile in North America

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ABSTRACT

The Catalan neuroscientist Antoni Grinyó Garriga was trained in the spirit of the Institut de Fisiologia in Barcelona, which impressed upon him an interest in research, focusing on the nervous system. In the 1930s, he was a lecturer in general physiology at the Universitat Autònoma de Barcelona, where he was responsible for the teaching of neurosurgery. A general surgeon in the early years of his career, he worked as a neurosurgeon during the Spanish Civil War. In 1939, he took exile in France and Venezuela, moving in 1941 to the United States, where he would remain for nearly 30 years. There, he combined neurosurgery practice with work in neurohistology, in which field he developed a method for staining oligodendroglia with silver ammino tungstate, which is named after him. He also researched radiology contrast agents used in angiography studies, and developed a percutaneous needle for arteriography, which also bears his name. He returned to Barcelona in the late 1960s, and died shortly thereafter.

KEYWORDS

Antoni Grinyó, neurosurgery, oligodendroglia, cerebral angiography, exile, United States

Introduction

In the orbit of Barcelona's Institut de Fisiologia, under the leadership of August Pi Sunyer (1875-1965), a generation of physicians and scientists took shape in the 1920s and 1930s; its natural development was truncated due to the disaster of the Spanish Civil War, which forced many of its members into exile. Such was the case of Antoni Grinyó, who is practically unknown in the world of Catalan and Spanish neuroscience, despite his undeniable merits. Though he was officially a neurosurgeon, his main focus was on neurohistology and neuroradiology research, taking particular interest in improving the neuroglial staining methods available at the time, and in the development of the emerging technique of cerebral angiography. It is hard to precisely establish the origins of his scientific and professional training before 1939; we must consider the influence of his colleagues, the neurosurgeon Adolfo Ley (1908-1975) and the neurohistologist Joan Bofill (1905-1970), and of the surgical department led by Antoni Trias (1892-1970) at Hospital Clínic (Barcelona), one of the first centres to perform cerebral angiography studies. After the trauma of the Spanish Civil War and its impact on his professional and family life, he enjoyed a fruitful professional and scientific career in the United States. He returned discreetly to Barcelona in 1968, probably sick, and died in late 1970.

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Material and methods

An extensive search was conducted of the literature on Antoni Grinyó, both online and in the archives of the University, Official College of Physicians, and Civil Register of Barcelona, as well as other archives. I also searched for personal accounts, such as that of Grinyó's daughter-in-law Anna Casellas. The literature search included the Catalan, Spanish, and English spellings of his name (Grinyó, Griñó, and Grino, respectively); Grinyó almost exclusively used the Catalan spelling in the last two decades of his life. The latter is the spelling used in this article, with Griñó and Grino only used when appropriate, according to the sources cited. This clearly would have been Grinyó's preference.

Development

A physiologist from a family of herbalists

Antoni Grinyó Garriga was born in Barcelona on 9 September 1903, into a family of shopkeepers who owned a traditional herbalist's store, founded in 1840: "L'Herbolari del Pi," later renamed "La Florida," was located on Calle Cardenal Casañas, beside Plaza del Pi. Antoni was the eldest of five siblings. The second-born, David (1908-1978), was a botanist, poet, and exponent of Catalan popular culture. The third brother, Arnau, worked as a physical education teacher, and coached the Spanish national rugby team in the 1960s.[1-4]

Antoni began his medical studies at the Universidad de Barcelona in the 1920-1921 academic year, achieving good results, and completed his studies in 1926. In 1927, he was awarded his medical degree with a grade of outstanding, and he earned his doctorate in Madrid in 1930.[1,5]

During his medical degree, he already established links with the Institut de Fisiologia in Barcelona, directed by August Pi Sunyer. Thus, his name appeared in the institute's report of research activity when he was a third-year student.[6] He was one of the youngest members of the group, and was interested in the physiology of the nervous system, according to his friend and contemporary Jaume Pi-Sunyer (1903-2000).[7]

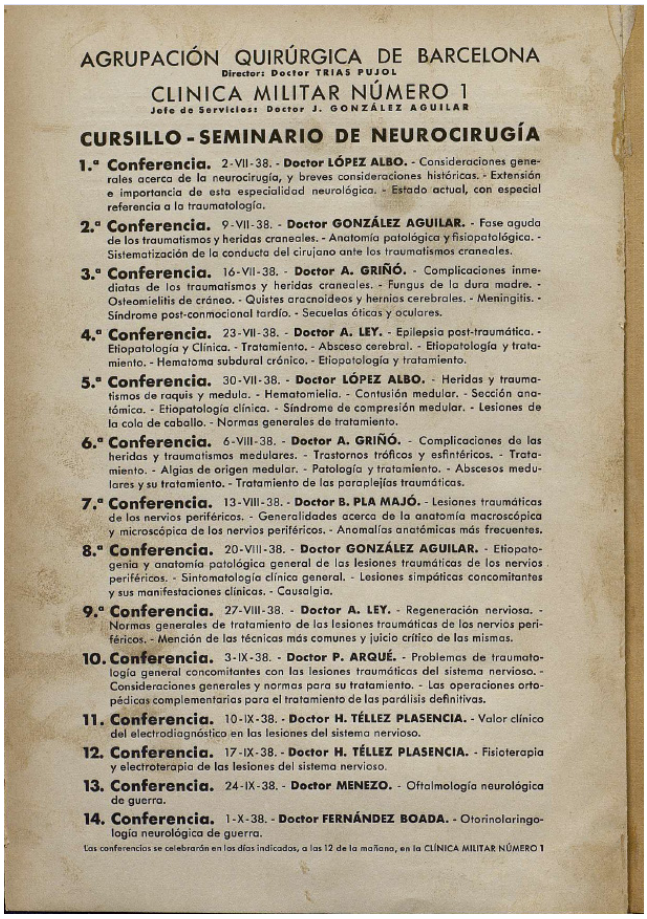
After graduating, he opened a private general surgery consultation, where he attended patients in the afternoons, and simultaneously worked as an intern at the surgical department of Hospital Clínic, a position he won in a competitive examination process.[5]

In 1934, he was employed on a five-year contract as assistant lecturer in general physiology at the recently created Universitat Autònoma de Barcelona. The contract was due to expire at the close of the 1938-1939 academic year, but he was unable to complete it as a result of the war.[1] At the university, he was responsible for teaching the course on neurosurgery.[8,9] On 11 June 1935, he participated in the end-of-year sessions of the neurosurgery course at Acadèmia i Laboratori de Ciencies Mèdiques de Catalunya, with a lecture entitled "Importància de l'examen precoç de les alteracions campimètriques i oftalmològiques en els tumors intracranials" ("The importance of early examination of visual field and ophthalmological alterations in intracranial tumours").[10]

Spanish Civil War

The neurologist Belarmino Rodríguez Arias (1895-1997) recounts how, at the outset of the conflict, the Hospital Clínic neurosurgeon Adolfo Ley Gracia created "a department of war neurosurgery, with the assistance of the university lecturer and general surgeon Antonio Griñó" at what is today Hospital del Mar. The department was established in the Municipal Psychiatric Emergency Clinic, which had been created in 1933 and renamed the Municipal Neurological Institute in 1936. The institute was directed by Rodríguez Arias and the psychiatrist Emili Mira (1896-1964), both of whom had lectured at the university since 1933.[11] Ley describes how he was head of neurosurgery at the centre from 1 December 1936, and simultaneously attended patients with nervous system injuries at the hospital installed at the Caixa de Pensions building in Montjuïc. In 1938, he transferred to the hospital of specialised surgery, installed at the former Orfelinato Ribas orphanage, and remained there after the fall of Barcelona, until the centre's closure in summer 1939.[12]

Grinyó was part of Dr Ley's surgical team, both at the Municipal Neurological Institute and at the Orfelinato Ribas, a centre specialising in neuro-oto-ophthalmology, where they shared their responsibilities with the neurologist and psychiatrist Wenceslao López Albo (1889-1944), director of Casa de Salud Valdecilla in Santander, who had fled to Barcelona to seek refuge. Grinyó probably also would have assisted Ley in attending injured patients at the Caixa de Pensions building in Montjuïc.[13] According to the official journal of the ministry of national defence, Grinyó was transferred with the rank of physician captain to the military hospital of the Barcelona Surgical



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1.ª Conferencia. 2-VII-38. - **Doctor LÓPEZ ALBO.** - Consideraciones generales acerca de la neurocirugía, y breves consideraciones históricas. - Extensión e importancia de esta especialidad neurológica. - Estado actual, con especial referencia a la traumatología.

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3.ª Conferencia. 16-VII-38. - **Doctor A. GRIÑÓ.** - Complicaciones inmediatas de los traumatismos y heridas craneales. - Fungus de la dura madre. - Osteomielitis de cráneo. - Quistes aracnoideos y hernias cerebrales. - Meningitis. - Síndrome post-conmocional tardío. - Secuelas óticas y oculares.

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7.ª Conferencia. 13-VIII-38. - **Doctor B. PLA MAJÓ.** - Lesiones traumáticas de los nervios periféricos. - Generalidades acerca de la anatomía macroscópica y microscópica de los nervios periféricos. - Anomalías anatómicas más frecuentes.

8.ª Conferencia. 20-VIII-38. - **Doctor GONZÁLEZ AGUILAR.** - Etiopatogenia y anatomía patológica general de las lesiones traumáticas de los nervios periféricos. - Sintomatología clínica general. - Lesiones simpáticas concomitantes y sus manifestaciones clínicas. - Causalgia.

9.ª Conferencia. 27-VIII-38. - **Doctor A. LEY.** - Regeneración nerviosa. - Normas generales de tratamiento de las lesiones traumáticas de los nervios periféricos. - Mención de las técnicas más comunes y juicio crítico de las mismas.

10. Conferencia. 3-IX-38. - **Doctor P. ARQUÉ.** - Problemas de traumatología general concomitantes con las lesiones traumáticas del sistema nervioso. - Consideraciones generales y normas para su tratamiento. - Las operaciones ortopédicas complementarias para el tratamiento de las parálisis definitivas.

11. Conferencia. 10-IX-38. - **Doctor H. TÉLLEZ PLASENCIA.** - Valor clínico del electrodiagnóstico en las lesiones del sistema nervioso.

12. Conferencia. 17-IX-38. - **Doctor H. TÉLLEZ PLASENCIA.** - Fisioterapia y electroterapia de las lesiones del sistema nervioso.

13. Conferencia. 24-IX-38. - **Doctor MENEZO.** - Oftalmología neurológica de guerra.

14. Conferencia. 1-X-38. - **Doctor FERNÁNDEZ BOADA.** - Otorinolaringología neurológica de guerra.

Las conferencias se celebrarán en los días indicados, a las 12 de la mañana, en la CLÍNICA MILITAR NÚMERO 1

Figure 1. Neurosurgery course/seminar (Barcelona, 1938).[16]

Regiment on 22 February 1938; on 15 March of the same year, he was urgently transferred to the surgical team of Adolfo Ley, at clinic 3 of the same regiment.[14,15] From 2 July to 1 October 1938, a course/seminar on war neurosurgery was organised at the Orfelinato Ribas; the sessions were coordinated by Joaquim Trias Pujol, head of the Surgical Regiment of Hospitals of Barcelona (Figure 1).[16] The course comprised 14 weekly lectures, two of which were delivered by Antoni Grinyó: one on the immediate complications of head trauma, and the other on complications in spinal cord injuries and trauma.[16,17]

In a curriculum vitae published in 1970, Adolfo Ley listed 30 distinguished medical professionals whom he had trained in neurology or neurosurgery; the first name on the list was Antoni Grinyó. The two shared an intense personal and scientific relationship between 1935 and 1939, the period between Ley's return after his neurosurgical training under Percival Bailey in the United States and the end of the Spanish Civil War. This collaboration led to an experimental study on the vegetative centres of the cerebral cortex, which was presented at the 7th Annual Meeting of the Spanish Association of Neuropsychiatry, held in Madrid from 2 to 6 December 1935: "Sobre la existencia de centros simpáticos corticales en relación con la motilidad del antro pilórico y la respiración (nota previa)" ("On the existence of cortical sympathetic centres related to pyloric antrum motility and respiration [preliminary report])".[12] The communication probably never appeared in written form, but Ley published the study in its entirety in 1945, appearing as the sole author.[18] López Albo also reported in the journal *Revista de Sanidad de Guerra* that, during a clinical session held on 17 June 1938, Ley and Grinyó presented two cases of "polyneuritis a frigori" that they were studying at their department.[19]

Throughout his life, Grinyó was sympathetic to Catalan nationalism, appearing in the press as a signatory to manifestos and participating in fundraising activities for political causes.[20,21] During the Spanish Civil War, he was affiliated with the Unified Socialist Party of Catalonia and the UGT trade union, and was a member of a cell of the party at the Universidad de Barcelona.[22,23] He was forced to take exile after the fall of Barcelona. His wife Montserrat Damians remained in Barcelona with their son, just a few months old. Years later, the marriage was annulled. Their son Raimon Grinyó Damians (1938-2015) was a distinguished Egyptologist and expert in Semitic languages.[4,24]

First years in exile

Following Catalonia's fall at the hands of the Nationalist rebels, various members of the Institut de Fisiologia, led by Jesús María Bellido (1880-1952), were welcomed to Toulouse by the physiologist Camille Soula (1888-1963) in mid-February 1939. In a letter dated 29 March, Bellido told the former mayor of Barcelona, Carles Pi Sunyer (1888-1972), that a large group of physiologists had formed around Soula and were working at his laboratory at the University of Toulouse medical school. One of the youngest members was Antoni Grinyó, who performed nervous system interventions in dogs. Two Saturdays per month, the Catalan physiologists and their colleagues from Toulouse met to discuss their respective

research.[25] Thanks to the manoeuvres of the professor of surgery Joseph Ducuing (1885-1963), Antoni Grinyó and his colleagues Bonaventura Benaiges (1909-2001), Joan Bofill, and Jaume Isern (1912-2006) were hired as *assistants étrangers* at the Centre régional anti-cancéreux de Toulouse. On 16 February 1940, the exiled Spanish physicians took centre stage in the monthly session of the Societé de Medicine de Toulouse, where Grinyó presented a case of traumatic pleural effusion.[26]

In April 1939, August Pi Sunyer, director of the Institut de Fisiologia in Barcelona, set sail with his family for New York, continuing on to Venezuela, where he would create the Caracas Institute for Experimental Medicine; the centre began operations in June 1940. With the fall of Paris and establishment of the Vichy regime the same month, panic took hold in the Spanish Republican refugee community in France, leading to a mass exodus. At that time, Benaiges, Bofill, and Grinyó emigrated to Venezuela, attracted by the figure of Pi Sunyer and probably following the same route. In 1941, Grinyó emigrated to the United States, whereas his colleagues remained in Venezuela, working in the pharmaceutical industry.[26,27]

Exile in the United States

The year after his arrival in the United Sates, Antoni Grinyó joined the academic world of that country. Between 1942 and 1944, he was a professor of neurology at the University of Tennessee College of Medicine in Memphis, where he conducted neurohistological research. In 1945, as a member of the university's laboratory of neuropathology and department of neurological surgery, and the Baptist Memorial Hospital in Memphis, he published an article on a new method for staining oligodendroglia and microglia.[28,29]

In 1944, he moved to New York, where until 1946 he was a neuropathology fellow at Bellevue Hospital, a centre linked with Columbia University.[29] The university's report of scientific activities in the 1940s mentioned "Dr Antonio Grino," who in the 1946-1947 academic year had conducted research on the nervous system, dedicating his study to the histochemistry of the glia and the use of contrast media in cerebro-roentgenology.[30] In June 1947, at the congress of the American Association of Neuropathologists, he presented his technique for metallic impregnation of the oligodendroglia in frozen or paraffin- or celloidine-embedded samples.[31]

Figure 2. A) Veterans Administration Hospital in Dearborn. B) Wayne State University in Detroit.

In July 1949, Grinyó and the ophthalmologist Edwin Billet (1918-2008) published a study on the use of cerebral angiography to diagnose orbital tumours. At that time, he was a member of the neurosurgery department of Montefiore Hospital and St. Vincent's Hospital, in New York. The authors acknowledged the advice of the head of neurosurgery at Montefiore Hospital, Leo Davidoff (1898-1975), one of the most distinguished neurosurgeons of the day.[32]

Between 1951 and 1952, Grinyó worked at the surgical department of the Western Reserve University School of Medicine and the Crile Veterans Hospital in Cleveland (Ohio). There, he and the renowned plastic and oral surgeon Clifford Kiehn (1907-2004) published an article on iliac bone grafts in the skull.[33]

In 1953, Antoni Grinyó was designated head of neurosurgery at the Veterans Administration Hospital in Dearborn (Detroit metropolitan area). The centre, also known as the Allen Park Veterans Administration Medical Center, attended military veterans from the state of Michigan. From 1954, he also worked as professor of neurosurgery at the Wayne State University medical school (Detroit) (Figure 2).[29,34] From that time, he signed all his studies with the Catalan spelling of his name, Grinyó, no longer using the English or Spanish forms.

In the United States directories of neurological surgeons between 1957 and 1964, he is listed as a resident of Dearborn; in 1968, he was listed as a resident of American Lake, in the Tacoma area (Washington State).[35-37] However, information from registers at the Veterans Administration centres suggests that Grinyó began working at the hospital in American Lake in 1962-1963, remaining there until at least 1968.[37-39]

Antoni Grinyó was an active member of the Catalan community in the United States. For instance, he was one of the speakers at a dinner held by the Catalan Centre of New York on 31 January 1948 to honour the surgeon Josep Trueta, who was returning to England after visiting the universities of Harvard and Yale.[40-42]

In the United States, Grinyó married a nurse, Mary Ella; the couple had no children.[4,39] The 1950 census lists him as Antoni Grinyó, married, resident in New York, working as a surgeon in private practice.[43] In an article published in 1968, he noted that his late wife Mary Ella had helped draft the manuscript, suggesting that she died shortly before the publication of the article.[39]

Antoni Grinyó was a member of the physicians' trade union Sindicat de Metges de Catalunya until 1939,[44] and also belonged to the American Medical Association, the Harvey Cushing Society, the Catalan Society of Biology,[29] and the Union of Spanish University Professors abroad.[45]

Return to Catalonia

According to some sources, Antoni Grinyó sporadically visited Catalonia from 1967, moving there permanently in 1971, and died in 1973.[46-48] In fact, he actually died on 16 December 1970, as recorded in the Civil Register of Barcelona. The document lists him as a 67-year-old widower, resident on Passatge del Patriarca, where he had lived before taking exile.[22,23,49] The cause of death was cardiac arrest.[24]

In Barcelona on 17 October 1968, Grinyó gave the inaugural lecture of the Catalan Society of Biology for the 1968-1969 academic year, addressing the oligodendroglia as a potential substrate of memory.[50]

On 19 December 1971, the neurosurgeon Adolfo Ley Gracia dedicated his admission speech at the Royal Academy of Medicine of Barcelona to the memory of Dr Antoni Griñó, whose humble friendship and loyal collaboration had decisively influenced the course of his life and career.[51]

Scientific activities

Study of vegetative centres of the cerebral cortex associated with gastrointestinal motility in dogs

Adolfo Ley reports that in 1935, shortly after his return from North America, he and Antoni Grinyó carried out the only basic research project he performed in his life. In 1933-1934, Ley had personally met John Fulton (1899-1960), James Watts (1904-1994), and Donal Sheehan (1907-1964), becoming interested in their discoveries on the central control of gastric and intestinal motility in primates,[52,53] and decided to replicate these studies in dogs upon returning to Barcelona. He was assisted in this task by the research skills of Antoni Grinyó, who actively participated in the experiments. The pair were supported by Antoni Oriol Anguera (1906-1996), professor of biochemistry at the Barcelona School of Agricultural Engineering, who advised them and made available his laboratory, the necessary instrumentation, and the 25 dogs used in the research. The study supported the previous findings of other authors on the control exercised by the sigmoid gyrus of the cerebral cortex and the tuberoinfundibular region of the hypothalamus over muscle tone and gastric peristalsis and, to a lesser extent, gastrointestinal transit. The authors presented preliminary data from the study at the December 1935 meeting of the Spanish Association of Neuropsychiatrists; the literature search yielded no written record, but Ley published the complete results of the study in 1945, signing as the sole author but acknowledging Grinyó's role in the research.[18] The outbreak of the Spanish Civil War a few months later, and Antoni Grinyó's exile, prevented them from continuing this line of research.

Neurohistological studies of the oligodendroglia

From the time of his arrival in the United States, Grinyó was particularly interested in the oligodendroglia, whose morphological secrets he sought to discover and which had not been sufficiently elucidated by the impregnation methods described to date, in particular the characteristics of their protoplasmic processes.[39,50]

In 1945, as a result of his research at the University of Tennessee, and having worked for two years with the Río-Hortega and Penfield methods, he published a novel technique that was useful in achieving specific, constant impregnation of the oligodendroglia and microglia in autopsy studies using formalin-fixed specimens, studied 15 days to one year post mortem.[28]

The staining method involved impregnation of nervous tissue with a silver ammino tungstate solution. The sample was first passed into a 3% glacial acetic acid solution for 30 minutes, to achieve an acidic pH, then into 1% hydrogen peroxide for ten minutes. Subsequently, the specimen was placed for no longer than 10-20 seconds in a bath of silver tungstate solution (Ag_2WO_4). This solution was obtained by mixing silver nitrate with sodium tungstate (both at 10%), with concentrated ammonia water added to dissolve the precipitate. Subsequently, the sample was reduced in 1% formalin and fixed in 2% sodium thiosulphate. This procedure fully stained the cells, revealing all their expansions, which in the case of oligodendroglia extended long distances from the cell body. It was also possible to observe the arrangement of chromatin in the nucleus of oligodendroglia and microglia. The procedure did not stain nerve cells and their axons, nor astrocytes.[28] However, Grinyó did not consider the method totally adequate as he also wished to use it in paraffin- and celloidine-embedded sections.[39]

He subsequently described the method at a meeting of the American Association of Neuropathologists in Atlantic City (New Jersey) in June 1947,[31] and once more at a meeting of the Harvey Cushing Society in Quebec in May 1955.[39,50] A written record exists of the first intervention, including a detailed description of the method and the comments of the attending experts. At this meeting, Grinyó once more addressed his staining method, which he now described as specific to oligodendroglia, in frozen or paraffin- or celloidine-embedded sections. The technique consisted in initially treating sections with distilled water containing two to three drops of acetic acid, to achieve a pH of 2.4. Sections were then passed into a 3% hydrogen peroxide solution for one second or less, then impregnated for no longer than 15 seconds in a silver tungstate solution containing two to three drops of aerosol IB (sodium diisobutyl sulfosuccinate) to reduce surface tension. The sections were subsequently placed in a formalin solution, achieving complete staining of the oligodendroglia.[31]

In 1968, he presented his definitive method for metallic staining of the oligodendroglia in the journal *Stain Technology*. Specimens were treated for three to five minutes with a 0.02% acetic acid solution to achieve a pH of 3.4, then with 3% hydrogen peroxide. Subsequently, they were placed for 15-20 seconds in a 10% silver tungstate solution, with the precipitate subsequently being dissolved with ammonia hydroxide; sections were then treated with 1% formalin and 5% sodium thiosulfate. For embedded specimens, a mixture of aerosols OT and MA (sodium dioctyl sulfosuccinate and sodium dihexyl sulfosuccinate, respectively) was used as a wetting agent. Grinyó described in detail the variations of the method according to whether specimens were frozen or embedded in paraffin or celloidine.[39]

He observed that oligodendroglial processes were extremely long (sometimes exceeding 100 μm) and surrounded myelin sheaths. Perivascular oligodendroglial cells were in close contact with vessel walls, which were surrounded by their cell body and processes. They also formed a fine, complex network around nerve cells and myelin sheaths. A single oligodendrocyte projected several processes to a vessel and, at the same time, to the nerve cell or myelin sheath. Grinyó thought that the oligodendroglia may act as a connection between nerve cells and myelin sheaths and vessels, playing an important role in brain metabolism. The technique was sufficiently specific to oligodendroglia, and did not stain nerve cells, whose form could be recognised due to the oligodendroglial network surrounding them. Astrocytes were not stained, or were poorly stained in the case of gliosis. The microglia and Schwann cells also displayed no staining (Figure 3).[39] Grinyó recognised that, although his method represented a step forward, it did not definitively solve the problem of staining oligodendrocytes.[31,39,50]

A key part of Antoni Grinyó's research work at the Veterans Administration Hospital in Dearborn from 1954 to 1961 was his study of the behaviour of oligodendrocytes and astrocytes in multiple sclerosis; as part of this research, he trialled different metallic impregnation

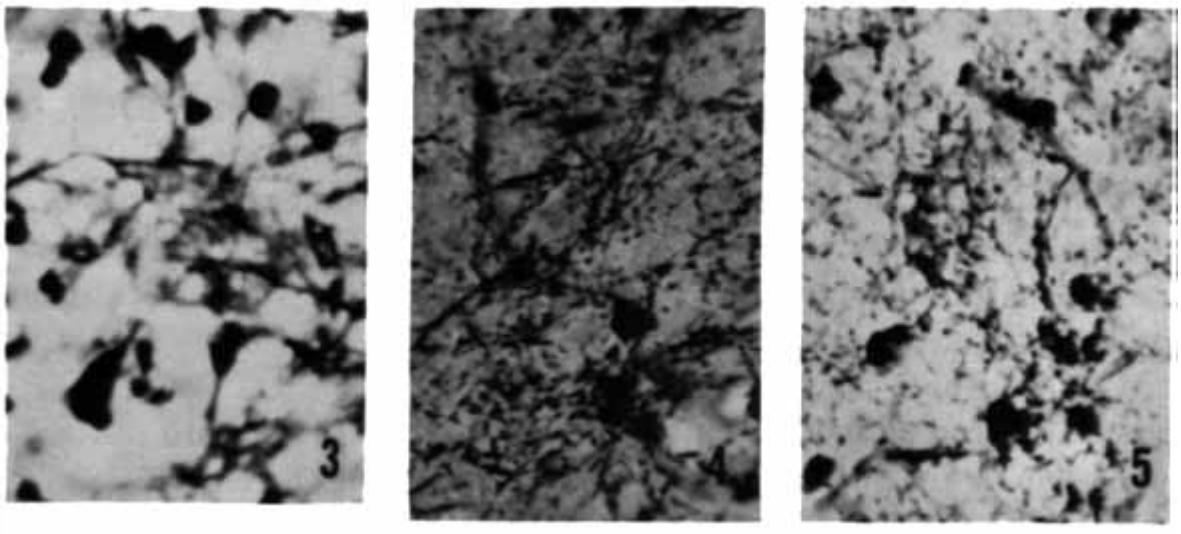

Figure 3. Frozen rat brain sections, fixed for ten days in Cajal formalin ammonium bromide. 3) Del Río-Hortega silver carbonate method. Only nerve cells and oligodendrocyte nuclei are stained. 4) Silver tungstate method. Perivascular oligodendrocytes, cytoplasm, and gliosomes are well stained. 5) Image from the same specimen as that shown in image 4); an area in which the perineural network is clearly shown.[39]

methods. Within this project, he also became interested in the effect of lysergic acid and other neurotropic substances on the neuroglia.[54-58]

The Hungarian neuropathologist Ferenc Gallyas wrote in 1979 that "Grino" had studied the impregnation of microglial cells with solutions containing sodium hydroxide, arsentate, molybdate, citrate, and tungstate at different concentrations, and that sodium tungstate facilitated the visualisation of microglial cells. Unfortunately, Gallyas does not provide a source supporting these claims.

Oligodendroglial function

In Grinyó's lecture in October 1968, opening the academic year of the Catalan Society of Biology, he recounted how he had been invited to participate in a lecture on the biology of the neuroglia and a neuropathological symposium on the neuroglia at the National Institutes of Health in Bethesda (Maryland) on 29 and 30 March 1956, with the contents published two years later.[50,58] At the meeting, the Harvard researcher Alfred Pope (1915-2009) had mentioned that neuroglial cells were ten times more numerous than neurons, although the structure and biological role of the former remained unknown.[59] He was also interested in the findings of Holger Hydén (1913-2000), who demonstrated that the glia contained large amounts of RNA, and that the RNA content of nerve cells increased when they were stimulated, whereas it decreased in the glia, suggesting that the two types of cells comprised a functional unit in which the glia could metabolise substances for nerve cells.[60] In his lecture, Grinyó also mentioned the experiments conducted by James McConnell (1925-1990), in which planarians were conditioned to a series of stimuli. Subsequently, he would grind the worms and feed them to unconditioned planarians, which responded faster to the same stimuli, as if they had eaten memory. The same response was observed when RNA from conditioned planarians was injected into unconditioned individuals.[61] In the light of the fact that oligodendrocytes contain large amounts of RNA, he imagined that these cells played an important role in memory mechanisms.[50]

Grinyó doubted that a cell type that is so widespread throughout the central nervous system and that surrounds nerve cells and vessels should be exclusively

involved in myelin production, a fact that had already been demonstrated in the years preceding 1968.[50,62] Despite this, he did not cease his research into the behaviour of oligodendrocytes, or astrocytes, in multiple sclerosis, a demyelinating disease.[54-56]

There is no evidence that Grinyó had received specific training in neurohistology prior to 1939. However, he was probably influenced by Joan Bofill, one of his closest colleagues at the Institut de Fisiologia and at the university, with whom he shared his exile in France and Venezuela. Bofill trained in neuropathology under Pío del Río-Hortega at the Residencia de Estudiantes in Madrid in 1926-1930,[63] and studied tissue culture techniques in Germany in 1930-1932, with grants from the Board for Study Extensions and the Rockefeller Foundation.[64] Furthermore, from 1937 he was professor of histology at the Universitat Autònoma de Barcelona.[65] In exile in Toulouse, he practised "microglia staining with new methods" at Hôpital La Grave, and was employed at the Centre Régional Anti-Cancéreux as a histopathology assistant.[25] At the 16 February 1940 session of the Société de Médecine de Toulouse, he spoke on the nature of a malignant neurinoma studied using the Río-Hortega method.[26]

The Grinyó method

The Grinyó (Griñó, Grino) oligodendroglia staining method was acknowledged and used by different neuropathologists over the course of several decades. In 1947, K. Lowenberg and L.D. Stevenson recognised that it offered significant advantages for impregnating embedded and frozen nervous tissue. Furthermore, it saved time and was able to reveal oligodendrocyte processes more specifically, as astrocytes were not stained.[31]

The method was strongly supported by Klaus-Joachim Zülch (1910-1988) and his colleagues at the Max Planck Institute for Brain Research in Cologne, who studied the neuropathology of brain tumours. They particularly used the technique to study experimental brain tumours induced in rats,[66-68] and in the World Health Organization histological classification of tumours of the central nervous system, in which Zülch was a key figure.[68-70] This differentiated visualisation of oligoglial elements was particularly valuable in the differential diagnosis of oligodendrogliomas, especially polymorphous tumours.[68-79] In the book edited by Zülch in 1961 on the classification of brain tumours, the Spanish neuropathologist Wenceslao Calvo (1921-2003) wrote that the "Grino" method was one of the best metallic impregnation techniques for characterising oligodendrocytes.[69]

In a 2019 book on the history of Spanish involvement in the discovery and characterisation of the glia in the central nervous system, including in the international context, Antoni Grinyó and his oligodendroglia staining method are not mentioned.[72]

Neuroradiology

In 1948-1949, while Grinyó was working at the neurosurgical department of Montefiore Hospital and St. Vincent's Hospital in New York, he and the young ophthalmologist Edwin Billet published an article on the diagnosis of orbital and intracranial tumours presenting with unilateral exophthalmos and vision loss. The examinations routinely performed when orbital tumour was suspected were simple radiography, retro-ocular air insufflation, surgical or aspiration biopsy, and occasionally pneumoencephalography. Grinyó and Billet proposed cerebral angiography as an alternative to the more invasive studies.[32]

The authors reviewed the history of brain angiography studies from the classical descriptions of António Egas Moniz (1874-1955)[73] and Antoni Trias,[74] of Barcelona, with whom Grinyó had worked, but argued that the technique was limited by a lack of safe and appropriate contrast media. Among these agents, they cited strontium iodide and sodium bromide, which were abandoned with the appearance of Thorotrast; the latter drug did not cause the adverse reactions associated with halogen derivatives, but was radioactive and remained in the body for years. This contrast agent had been surpassed by Diodrast (iodopyracet), the medium used by Grinyó. The percutaneous puncture was performed with a modified gauge 17 Cournand needle, 3.5 inches in length, which was specially made for them by the company Becton & Dickinson. The three cases were studied in 1947-1948 at Montefiore Hospital, and the authors were advised by the head of neurosurgery, Leo Davidoff. The tumours were a sphenoidal wing meningioma, which was treated surgically, and two orbital tumours: a haemangioma, treated surgically, and a possible haemangioma, treated with radiotherapy. The authors argued that angiography was the safest and most effective technique for the differential diagnosis of orbital and cerebral tumours, and was preferable over pneumoencephalography; in the case of

Figure 4. Arteriography image (Diodrast contrast medium) of a right orbital tumour.[32]

orbital tumours, it was also preferable over needle biopsy and orbital air insufflation (Figure 4).[32] They refer to a future publication by Grinyó, which would describe the advantages of using their needle in angiographic procedures, but which appears never to have been published.[32]

The article by Grinyó and Billet was the first published study to use angiography in the diagnosis of orbital tumours.[75] They noted the importance of carotid arteriography for visualisation of the ophthalmic arterial complex.[76,77] This examination was particularly valuable for differentiating tumours of the optic nerve from angiomatous or metastatic lesions, which presented greater vascularisation.[78]

The percutaneous arterial puncture needle described in the article was later used by other neuroradiologists, who called it the "Grino needle" or the "Cournand-Grino needle" (Figure 5),[79] as it was a modification of the needle used by the French angiologist André Cournand (1895-1988) in his studies of pulmonary and cardiac catheterisation at Bellevue Hospital in New York, where he coincided with Grinyó. Cournand won the 1956 Nobel Prize in physiology or medicine for his pioneering work in cardiac catheterisation.[32,80] The needle was widely used in angiography studies between the 1950s and the 1970s, for injections into the subclavian, carotid, and femoral arteries, as well as the femoral vein.[81-85]

According to a book detailing the scientific activities of the neurology department at the University of Columbia College of Medicine in the 1940s, "Dr Antonio Grino" researched glial histochemistry and the use of contrast media in cerebro-roentgenology in the 1946-1947 academic year.[30] Records of scientific activity at the Veterans Administration institutions mention that Antoni Grinyó, in Dearborn in 1955, began studying chelating agents and heavy metal salts to observe their physiological, toxic, and roentgenological properties. He trialled various chelating agents to dissolve heavy metal salts, particularly lead bromide and lead nitrate, which were difficult to dissolve. These mixtures were injected into the nervous system of laboratory animals; they were found to be sufficiently radiopaque to be visualised in the vascular system, and no external adverse effects were detected. Grinyó also conducted chemical experiments to determine the pathway and rate of clearance of these compounds in the organism.[86,87] The literature search yielded no neuroradiology publications derived from Grinyó's research at Columbia University or at the Veterans Administration.

Frontal iliac bone grafts

Grinyó co-authored an article published in May 1953 on the use of iliac bone grafts as a replacement for the tantalum plates used after the Second World War to correct skull defects and deformities caused by gunshots, particularly in the frontal and supraorbital regions, which could cause infections, local pain, headache, epilepsy, and other symptoms. The lead author was the plastic and oral surgeon Clifford Kiehn. At the time, Grinyó was still publishing under the English spelling of his name (Grino), and belonged to the department of surgery at Western Reserve University and the Crile Veterans Hospital in Cleveland (Ohio). The authors observed that the iliac bone was an excellent medium: it was of sufficient size to correct the defects, and its shape was well-suited to the frontal region, with the crest serving as

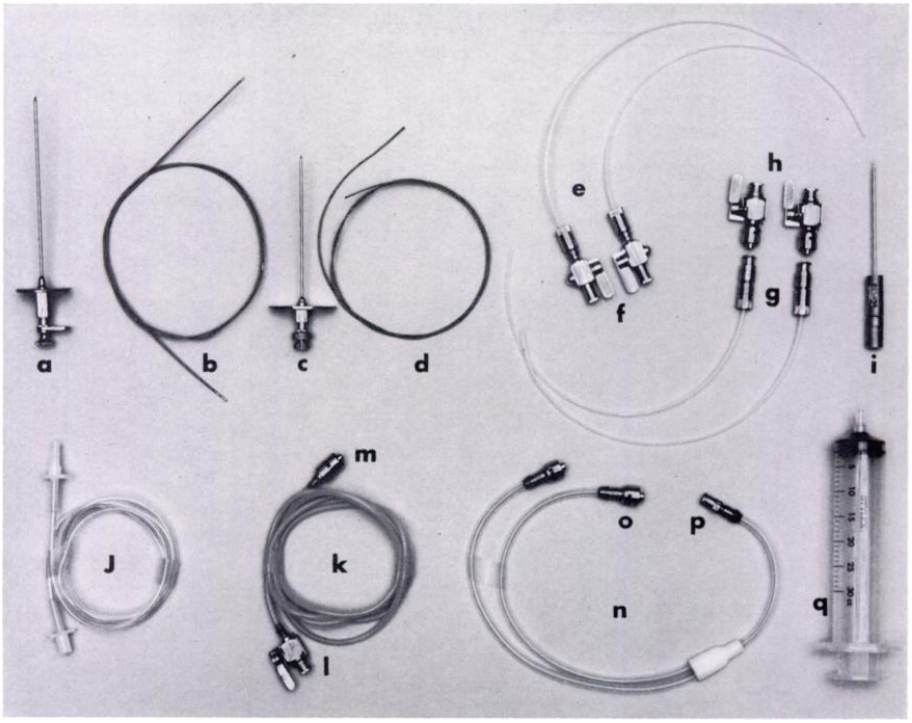

Figure 5. Instrumentation used in direct intraclavicular catheterisation of the subclavian artery: a) Cournand-Grino needle; b) flexible gauge 19 metal guidewire, which fits inside the needle.[79]

a supraorbital ridge and the ala used in the frontal and parietal regions. It presented rapid vascularisation and good viability. In the article, they reported ten cases who had undergone the procedure in the period 1950-1952.[33]

Neurolathyrism

Another subject Grinyó researched at the Veterans Administration was neurolathyrism. He began studying the disease in 1961, still at Dearborn,[56] and continued this research in 1962-1963 at the hospital in American Lake.[38,56] The literature search yielded no publications on the subject, and we do not know the content of his research or whether he studied the behaviour of the oligodendroglia in patients or in rodents, the animal model of the disease. We cannot rule out the possibility that he was influenced by the neurologist Carlos Oliveras de la Riva in the 1940s; Oliveras was very close to Adolfo Ley, and made important contributions to our understanding of the disease. The grasspea neurotoxin L-β-ODAP has been shown to have a gliotoxic effect, particularly on oligodendrocytes and the myelin sheath, although these findings were reported in the 1990s, after Grinyó's death.[88]

Conclusions

Antoni Grinyó, like so many other colleagues from his generation, had to leave everything behind after the Spanish Civil War and leave for exile, surrounded by uncertainty. In Grinyó's case, despite his leftist past, he carried out the majority of his professional and scientific activity in the competitive, politically conservative world of Cold-War America, reaching heights that would have been beyond his grasp had he stayed in Catalonia during the Franco regime.

Though his career shifted from general surgery to neurosurgery, his main scientific legacy was in the field of neurohistology, with his studies on the neuroglia. He also distinguished himself in the field of neuroradiology through his efforts to improve angiographic techniques

and contrast media. His name is associated with the silver ammino tungstate oligodendroglial staining method, which represented an improvement on existing techniques, as well as the needle he developed for percutaneous arterial puncture. He should also be recognised for having pioneered the use of angiographic media in the diagnosis of orbital tumours.

Some work is yet to be done to more completely describe the life and work of Antoni Grinyó, but now is the time to restore him from the ostracism to which he was relegated by historical circumstance, returning him to his rightful place. Future studies should include the accounts of other people who knew him and search for additional documents and publications not identified in the present study.

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Conflicts of interest

The author has no conflicts of interest to declare.

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