History of Neuroscience: Mesoglia and Microglia

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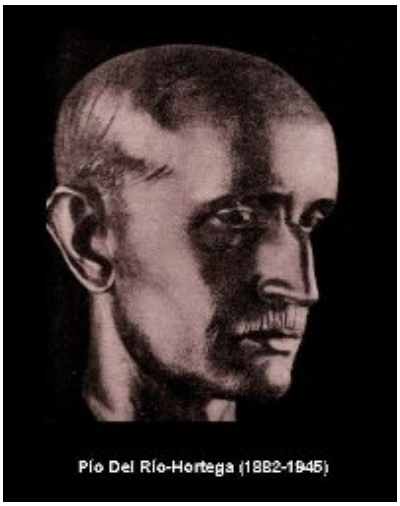
Microglia are mononuclear phagocytes that reside within the central nervous system (CNS). They differ from macroglia (astrocytes and oligodendrocytes) in terms of their origin, phenotype and functions, but more closely resemble tissue-resident macrophages in all these aspects. The principal role of microglia is to provide a first line of defence against pathological insults at this primary site. Modern consensus holds that microglia are of myeloid origin, much like tissue-resident mononuclear phagocytes within other organs, and arise during fetal development from progenitors in the yolk sac, liver or spleen or from mesenchymal tissues surrounding the nervous system that subsequently seed the CNS during gestation and perinatally, and differentiate morphologically to ramified and immunophenotypically suppressed adult varieties (20, 31). These intriguing and controversial cells have been the focus of intense scientific research for the past two decades, and the subject of many recent reviews to which the reader is referred (8, 11, 12, 14-16, 18, 20-22, 24-27, 31-34, 54-57).

Prior to the twentieth century, the nervous system was considered to be composed of two types of cell, which differed in form and function, namely nerve cells and neuroglia (interstitial cells of the nervous system). Following the discovery of neuroglia by Virchow in 1846, numerous attempts were made to demonstrate these cells in situ. However, belief had been prevalent for some time that mesodermic elements also penetrated the nervous tissue both during embryonic development and under pathological conditions, and could subsequently transform to a population of neuroglia (34). Scholars of the late nineteenth century generally adhered to three principal theories regarding the origin of 'neuroglia' as being derived: (i) solely from ectoderm, or otherwise from the primitive medullary canal, (ii) in equal part from mesoderm and ectoderm, or (iii) from the mesoderm. The idea that neuroglia in man could be derived from mesodermal tissue was further emphasized by Eichhorst towards the end of the nineteenth century (10). He noted that 'neuroglia' were absent from the white matter of the spinal cord until the fourth month of fetal human life, when extravasating leukocytes began to migrate and ramify, and became immobile upon reaching their final destinations. Such terms as 'mesoglia', and later 'third element of the nervous system', were first introduced by W. Ford Robertson (52, 53) in 1900 and Santiago Ramon y Cajal (5-7) between 1913 and 1920 respectively, to define phagocytic mesoderm-derived elements within the nervous system, taking into account their separate origins from neurons and neuroglia (a term predominantly designating astrocytes). Between 1919 and 1921, this nomenclature was later amended by del Rio-Hortega (37-41) to 'microglia' in order further to discriminate between true mesodermal elements and oligodendrocytes, previously also regarded as a component of 'mesoglia'. This particular contention sparked much controversy among del Rio-Hortega's peers and resulted in an escalation of fruitful research throughout Europe that eventually declined up to the outbreak of the Second World War. The post-war years were a period during which the very existence and nature of microglia were cast in doubt until, in the 1960s, a new cohort of investigators realized the potential that is now commonly ascribed to microglia as 'intrinsic immune effector cells of the CNS' (12).

We owe a considerable amount of our knowledge of microglia to the discoveries of Pio Del Rio-Hortega (36-50) (Figures 1 and 2) as well as that of his mentor Santiago Ramon y Cajal (5-7) and to their predecessor William Ford Robertson (52, 53).



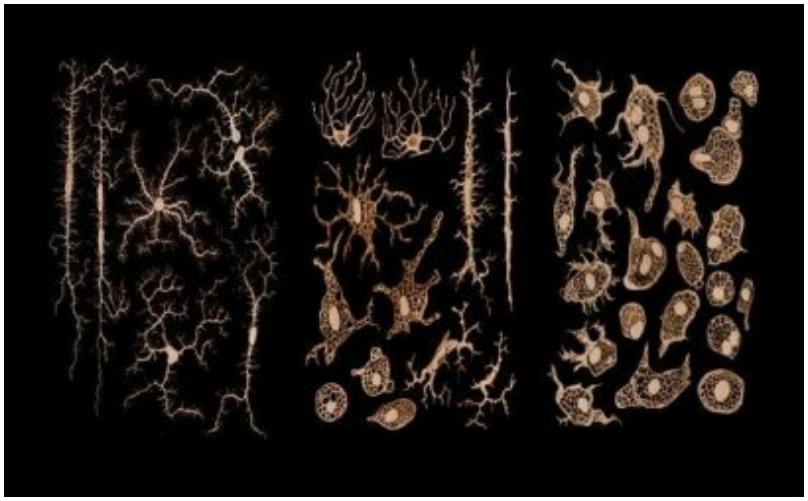


Figure 1: Figurehead of Pio del Rio-Hortega (1882-1945) with examples of his illustrations of human microglia (left plate), different cellular types of mesodermic origin (middle plate), and final stages of granulo-adipose bodies (right plate), and extracts regarding the forms and origin of microglia quoted from del Rio-Hortega, 1932 (46).

"The microglia or 'mesoglia' is of mesodermal (meningeal) origin, possesses liberal ramified expansions and displays migratory and phagocytic activity. It is more abundant in grey matter than in white, and is found in the general neuroglia-neuronal framework as an annexed element. By reason of its difference in characteristics and origin from nerve cells (first element) and neuroglia (second element), the microglia constitute the true 'third element of the CNS' and it is necessary to separate in all descriptions, microglia from the classical neuroglia, to avoid confusion.

"According to all indications the microglia is formed through migration of embryonic corpuscles from the pia into the nerve centres. These corpuscles are morphologically similar to lymphocytes and are probably homologous with the elements described in connective tissue … in addition to this origin, the only one that can be observed during intrauterine life and the early days of postnatal life, microglia may eventually arise from other related elements, chiefly the blood mononuclears. There is however, no evidence for this point. There are only indications and the belief is based on the similarity of certain amoeboid forms and definite activities (macrophagia) of the microglia and the monocytes … "

Born in Portillo (Valladolid, Spain), Pio del Rio-Hortega studied medicine at Valladolid (1898-1905), and obtained doctorate in Madrid (1908). Became a member of Cajal's staff, working in close association with Achúcarro, Tello, Lafora and de Castro. His latter days were spent in Buenos Aires with Polak. He set to work on determining the nature of Cajal's 'third element'. In 1917 he described his new ammoniacal silver carbonate method (an adaptation of Bielschowsky's stain), and in 1919-1921 announced that the element consisted of two types of cell, to which he gave the names, microglia and oligodendroglia. His classical work on the histogenesis of microglia appeared in 1921. He turned to pathology in the early 1930s, doing important work on meningeal and brain tumours (extracts from Guide to the Exhibit on the History of

Neuropathology' by W. Haymaker MD, Washington, DC, 1948).

These three luminaries, together with a cavalcade of peers between 1900 and 1940, laid the foundations for our contemporary views of the microglia. Many of the original articles of this period, a significant proportion written prior to the Second World War, have not been translated into English, and therefore much of the pioneering thoughts and views have remained unknown over the intervening years. A brief chronology and discussion of these papers and the research on microglia up to the 1980s, has recently been published in the *Journal of the History of the Neurosciences*,* (34) in order to bring these key articles to the attention of the present-day audience.

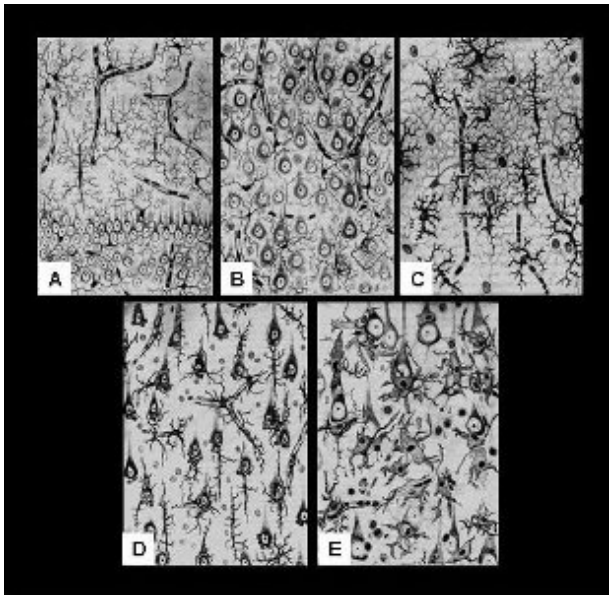


Figure 2: The different morphological states of microglia in the normal brain and in diseased states.

A. Distribution of microglia in the cerebral cortex of the rabbit. The various forms of microglial corpuscles can be seen in relation to vessels (vascular satellites) and nerve cells (neuronal satellites). **B.** Distribution of microglia in the stratum radiatum of the normal rabbit. Note the morphological variation of microglial corpuscles and their relationship with vessels. **C.** Characteristics of microglia in the stratum radiatum of a rabbit with chronic infectious disease. Note the enlargement and spinal aspect of cellular processes. **D.** Characteristics of microglia in human cerebral cortex in a case of subacute meningitis. Note the formation of rod cells. **E.** Microglia in the cerebral cortex of a rabbit in the proximity of a lesion site produced two days after a wound puncture with a hot needle. Observe the unusual, monstrous aspect of the microglial cells that adopt globular and laminar forms (adapted from del Rio-Hortega, 1919 (37), modified and reproduced with permission from Rezaie and Male 2002 (34), copyright Swets and Zeitlinger).

The literature on mesoglia and microglia in the twentieth century is presented pictographically in Figures 3 and 4.

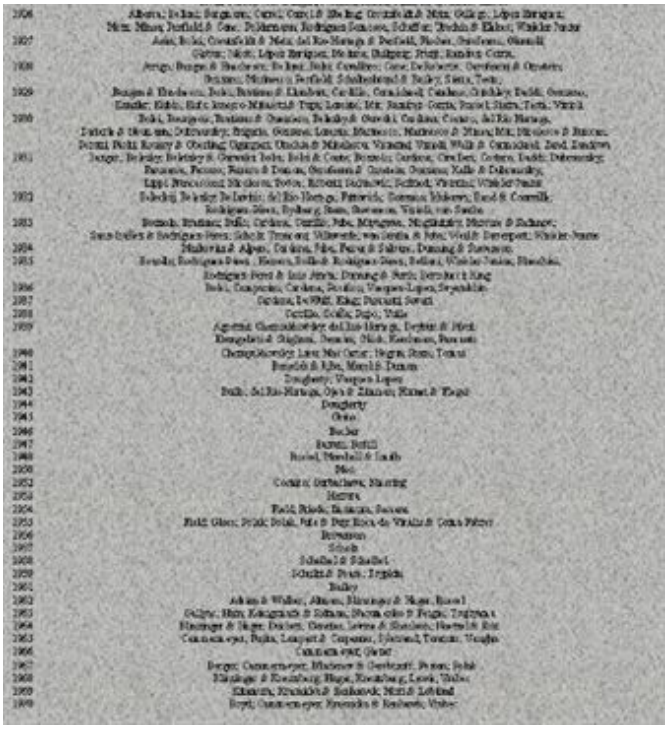
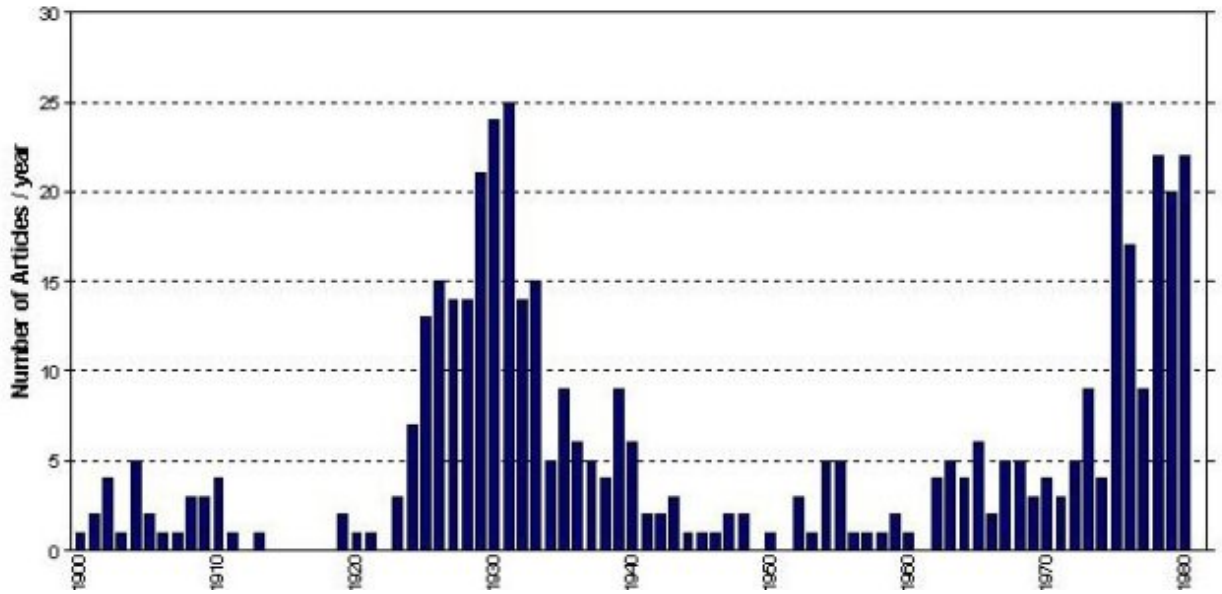


Figure 3: A chronology of mesoglia and microglial research from 1841 to 1970 (reproduced with permission from Rezaie and Male 2002 (34), copyright Swets and Zeitlinger).

Several reference resources and databases (19, 23, 30, 35, 51, 58) were consulted together with comprehensive cross-referencing, in order to formulate this presentation. From these figures, it is evident that the subject of microglia received considerable attention around 1930 following the studies of del Rio-Hortega, and was once more revived fifty years on in 1980 (Figure 4).



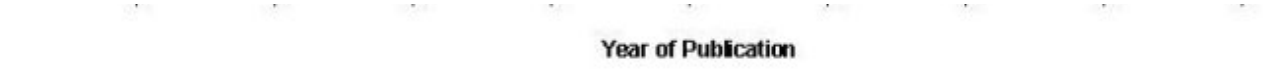


Figure 4: Ictographical representation of the literature on mesoglia and microglia from 1900 to 1980 (reproduced with permission from Rezaie and Male 2002 (34), copyright Swets and Zeitlinger).

From the late 1980s the literature has expanded at an almost exponential rate, as research in the neurosciences has gained momentum (17) (Figure 5). In particular, the importance of microglia as useful diagnostic markers of neuropathology and more specifically their immunoregulatory roles have gained much precedence in the neurosciences (21). The first international symposium on microglia was held in Munich, Germany nearly a decade ago (17, 28), two special issues of the journal 'Glia' (14, 15), and separately a pictorial (57), have been specifically dedicated to these cells, and more recently in 1999, a call for research proposals was put forward by the National Institute of Health in the United States, specifically to address the origin, pathophysiological and functional roles of microglia within the CNS (29).

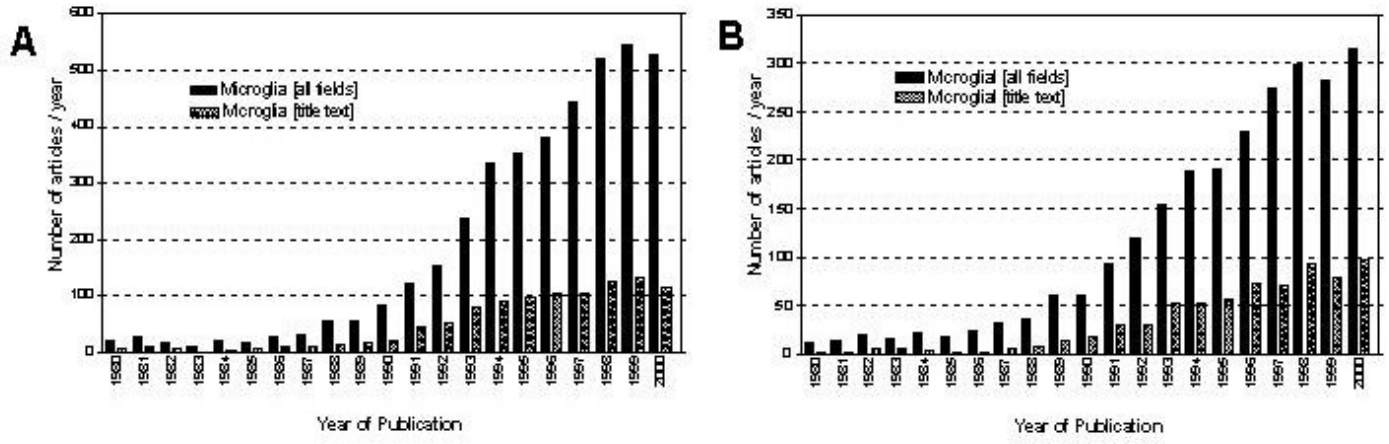


Figure 5: Pictographical representation of the literature on microglia from 1980 to 2000 (reproduced with permission from Rezaie and Male 2002 (34), copyright Swets and Zeitlinger).

Having surveyed the history behind the origin, forms and functions of these cells (34), it is apparent that the extent to which today's research is directed at questions first raised nigh on a century ago and earlier is quite remarkable. The significance of these earlier contributions cannot be overemphasized in an age when

ever-advancing techniques and accelerated publications have created a somewhat misguided tendency to neglect any research completed more than a few years earlier and to brand these as already 'dated'. Yet it is these same innovative, exciting and sophisticated technical advances that are beginning to provide answers for contemporary scientists.

Considering our current wealth of knowledge regarding the diverse roles of microglia in health and in disease (8, 11, 22, 25-27), and with new technological advances that enable us to visualise and monitor these cells directly in vivo in live patients (4, 13) the challenge that now lies ahead is to manipulate these cells for therapeutic approaches in neurological disorders. For example, as a potential means for delivering drugs to the CNS (1, 3) in cell transplantation (9), or for providing neuroprotection (55), and promoting the regeneration of neurons (2, 24, 56). Tapping into this potential will be the exciting prospect for research on the microglia as we move forward through the twenty-first century.

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