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The first Norwegian doctorate in multiple sclerosis

IN BYGONE DAYS

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The story of research on multiple sclerosis in Norway starts in 1945 at a private Catholic hospital in the town of Hamar, where the ophthalmologist Marius Haarr was treating patients with retinal periphlebitis and neurological symptoms. He completed his doctoral degree while raising two young children as a widowed father.

Figure 1 Marius Haarr's doctoral defence at Gamle Festsal auditorium in 1952. Photo: Aftenposten

'In 1945, a patient with an interesting clinical picture was admitted to St Torfinn Hospital in Hamar... Some time later, I found abducens nerve palsy in a patient who had had retinal periphlebitis two years earlier. It was treating these two patients that gave me the idea for my work. Are there disorders of the central nervous system that could be due to a cerebral periphlebitis?' (1)

In 1951, Marius Haarr (1908–1999) published the first Norwegian doctoral thesis on multiple sclerosis (MS): *Periphlebitis retinae in multiple sclerosis – a clinical examination* (1). He defended his thesis the following year (Figure 1). Haarr had examined more than 300 MS patients and found inflammation along the blood vessels in the retina in almost a third. Looking back, his observations appear to be both thorough and staggering, and the interpretation to be insightful (2–5). Marius Haarr was bestowed the Norwegian Candidate of

Medicine qualification (cand.med.) at the University of Oslo in 1935, and after practising psychiatry and working as a district physician, he worked as a volunteer at the Department of Ophthalmology in Ullevål Hospital in 1942. Before becoming a specialist in ophthalmology in 1948, he worked at St Torfinn, a private eye hospital, and the ophthalmology departments in Bodø and at Rikshospitalet. Following stints in the town of Molde and at Ullevål Hospital, he was appointed head senior consultant in the Department of Ophthalmology in Ålesund in 1952 and remained in the post for many years (6).

Although the eye is often described nowadays as the window to the brain, Haarr has been forgotten despite being one of the pioneers in examining multiple sclerosis through the eye. Haarr is not cited in literature reviews about the very condition that he was one of the first to write about.

Finding in the fundus

In a note to his children and grandchildren from around 1995, Haarr wrote that many years would pass from the time he saw the first patient with striking striped spots on the retina and concomitant neurological symptoms, until he initiated a systematic study of this phenomenon:

Fig. 1.

Venenettet i venstre øyebunn med perifle-
bittiske infiltrater. Kasus 15.

Figure 2 From Marius Haarr's doctoral thesis

'What interested me was, what did it look like in his brain? What we call the retina of the eye is nothing more than a visible part of the brain. Was there a nervous system disorder with varying neurological deficits that could be compatible with the ocular fundus picture I had seen? The only thing I could think of in my ignorance was multiple sclerosis.'

Haarr knew that the lesions of multiple sclerosis were caused by lymphocytes that migrate across the blood-brain barrier around venules in the brain and spinal cord. He had also read literature that described similar lymphocyte

infiltration around blood vessels in the periphlebitis retina (1). His hypothesis that the changes in the retina reflect the lesions in the brain in multiple sclerosis was therefore well-founded.

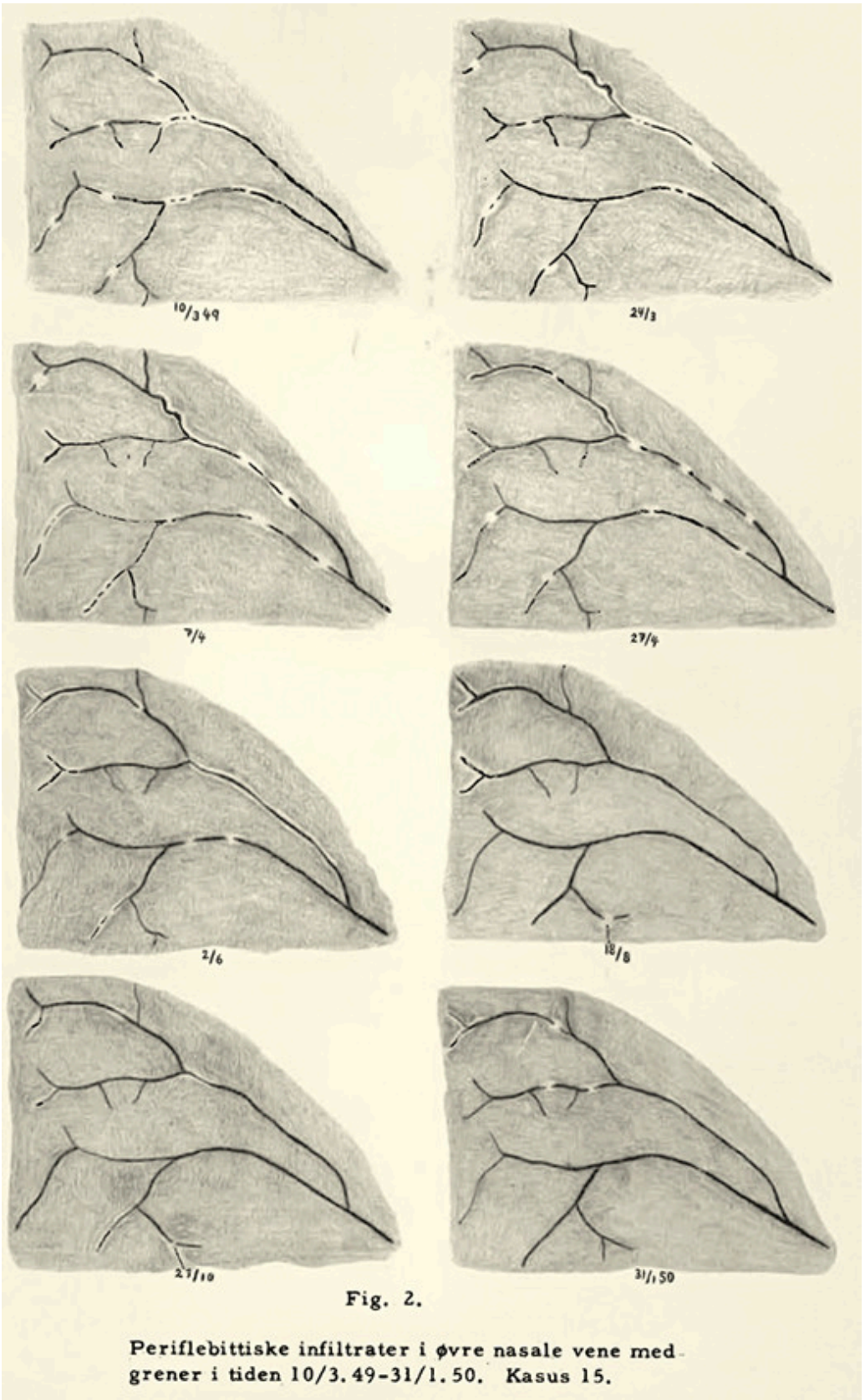

Figure 3 From Marius Haarr's doctoral thesis

From 1947 to 1950, Haarr examined 303 patients with multiple sclerosis and 225 control patients with other neurological disorders (including three 'morbus nullus'). The patients were recruited at Ullevål Hospital and Rikshospitalet in Norway, as well as Fredriksberg Hospital, the Military Hospital, Nørre Hospital, Copenhagen Municipal Hospital and Odense County and City Hospital in Denmark. His findings were checked by colleagues where this was possible. However, many patients were examined at home, which meant that perimetry visual field tests could not be performed and there were no colleagues to check the findings.

Haarr found inflammatory infiltrates around the retinal veins in 23 % of the multiple sclerosis patients and 3 % of the control patients (Figure 2). Eighteen uncertain findings were regarded as negative. Active periphlebitis occurred most frequently in those who had had multiple sclerosis for less than 10 years, while the changes had mostly 'dissipated' in cases exceeding 10 years. Haarr examined 24 of the patients several times (Figure 3); 'Case no. 3' was examined a total of 36 times over a period of 40 months. This enabled him to describe how exudative inflammatory changes developed around the venules over the course of several weeks and in some cases receded.

> ***«There are therefore strong indications that Haarr was right and that the lesions in the brain and in the retina have the same cause»***

Haarr considered there to be two possible explanations for the frequent occurrence of retinal periphlebitis in multiple sclerosis: the inflammatory infiltrates in the ocular fundus could either have the same cause as the lesions in the brain, or be sequelae to these (2). He believed there to be a strong argument for the common cause explanation; both the blood vessel changes and the lymphocyte infiltration were relatively similar. He was also aware that the American immunologist Thomas Rivers had recently developed experimental allergic encephalomyelitis (EAE) – which has many similarities to multiple sclerosis – through immunisation with brain tissue (1, 7). However, Haarr pointed out a significant difference: the nerve pathways in the retina are not myelinated, and cannot therefore become demyelinated, which is characteristic of both multiple sclerosis and EAE. He thereby indirectly anticipated the subsequent critique of the EAE model, which described multiple sclerosis as an autoimmune reaction to myelin (8). It has since been demonstrated that there is a common genetic predisposition for uveitis and multiple sclerosis, and that uveitis and multiple sclerosis can occur simultaneously in the same experimental animal model (9). There are therefore strong indications that Haarr was right and that the lesions in the brain and in the retina have the same cause.

Challenging working conditions

The systematic study of retinal periphlebitis was Haarr's own idea, and he carried it out without a supervisor. He performed his doctoral work in his spare time whilst employed in a full-time clinical position at Rikshospitalet. He also

had a study period in Denmark, where he examined patients at hospitals and nursing homes. He was widowed in 1948, becoming the sole carer for his daughters Anne-Marie (born in 1938) and Elisabeth (born in 1945) while working on his doctorate. Anne-Marie talks about housekeepers and strained finances during a period marked by challenges for her father, until he was appointed senior consultant in Ålesund in 1952. He did not pursue an academic career following his doctorate, but was a corresponding member of the National MS Society and published several clinical works (2, 3, 10)-(12).

Fame and oblivion

Haarr was not the first to link retinal periphlebitis to multiple sclerosis. The American ophthalmologist Charles Wilbur Rucker described the same clinical picture in the mid-1940s (13) and defended his thesis on *Retinopathy in multiple sclerosis* in 1947 (14). Haarr gave a thorough account of Rucker's findings in his own thesis and pointed out that his own original contribution was his longitudinal observations (Figure 3). Rucker for his part credited Haarr for discovering the link between multiple sclerosis and retinal periphlebitis at about the same time and independently of himself. In 1971, Rucker wrote to Haarr: 'Am I not correct in believing that you discovered this fundus picture quite independently, and that I just happened to stumble across it a few years before you did?'

> ***«The lack of photo documentation and the fact that his work was published as part of a Norwegian monograph may partly explain why Haarr is rarely cited»***

Rucker carried out his doctoral work at the Mayo Clinic in Minnesota, where he later became a professor and head of the ophthalmology department (15). He had access to modern photographic equipment and published photographs of his findings in the prestigious Journal of the American Medical Association (JAMA) (13). However, Haarr did not have access to photographic equipment. He used drawings to document his findings, which he first published in Norwegian in 1951 in his doctoral thesis. He also subsequently published the findings in English-language journals, including at the invitation of the Danish multiple sclerosis pioneer Torben Fog, who was editor of Acta Neurologica et Psychiatrica Scandinavica (2, 5). The lack of photo documentation and the fact that his work was published as part of a Norwegian monograph may partly explain why Haarr is rarely cited. However, this is not the whole story, as Rucker's work on retinopathy in multiple sclerosis is also often neglected (16). An alternative explanation is the common desire to refrain from citing 'outdated' references in a bid to appear up-to-date. Haarr himself avoided this trap and cited the first published case of periphlebitis retina from 1891 (1).

Multiple sclerosis and uveitis

We now know that there is an association between both periphlebitis and other forms of uveitis and multiple sclerosis. Intermediate uveitis is considered to be the most common manifestation and often occurs as a low-grade, chronic inflammation of the peripheral part of the retina and vitreous body (9). Multiple sclerosis-associated retinal periphlebitis is most often an asymptomatic finding, but visual disturbances are occasionally seen with development of retinal ischemia and neovascular complications. The prevalence of uveitis in multiple sclerosis patients is estimated to be about 1 %, i.e. significantly lower than the figures from both Haarr and Rucker 70 years ago. However, retinal periphlebitis is associated with higher multiple sclerosis activity (17). The first clinical trials using adrenocorticotropic hormone as anti-inflammatory treatment for multiple sclerosis were described by the previously mentioned Torben Fog in 1951, the year Haarr published his thesis (18). The high prevalence in historical studies may reflect the lack of disease-modulating treatments for multiple sclerosis at the time or the sample of hospitalised patients with severe illnesses.

Three pioneers

In 1952, the year when Haarr defended his thesis (Figure 1), Canadian Roy Laver Swank published the first epidemiological study of multiple sclerosis in Norway in the New England Journal of Medicine, with a Norwegian, Julie Backer, as co-author (19). Swank postulated that a diet high in dairy products and animal fats predisposes a person to multiple sclerosis. He believed that Norway, with its distinctive topography and heterogeneous living conditions, was best suited for such a study. The study found a low prevalence of multiple sclerosis and a low intake of dairy products and animal fats along the coast, which supported Swank's hypothesis. The study in Norway was an important catalyst for 'the Swank diet' and the Swank MS Foundation, which is still going strong in the United States. However, the authors discussed the possibility of selection bias. The first neurological ward outside Rikshospitalet was first established in Bergen in 1952, so the threshold for being diagnosed with multiple sclerosis in the fishing districts in western and northern Norway was therefore most likely high. Nevertheless, Swank – and not Haarr – is often credited with initiating modern multiple sclerosis research in Norway.

This is perhaps not so strange – Swank tested an original hypothesis, used the best epidemiological methods available and worked with Julie Backer, who was a leading expert on health statistics. Publication in the New England Journal of Medicine also has a greater impact than a Norwegian monograph. On the 70th anniversary of multiple sclerosis research in Norway, it is time to bring the pioneer Marius Haarr out of oblivion (Figure 4).

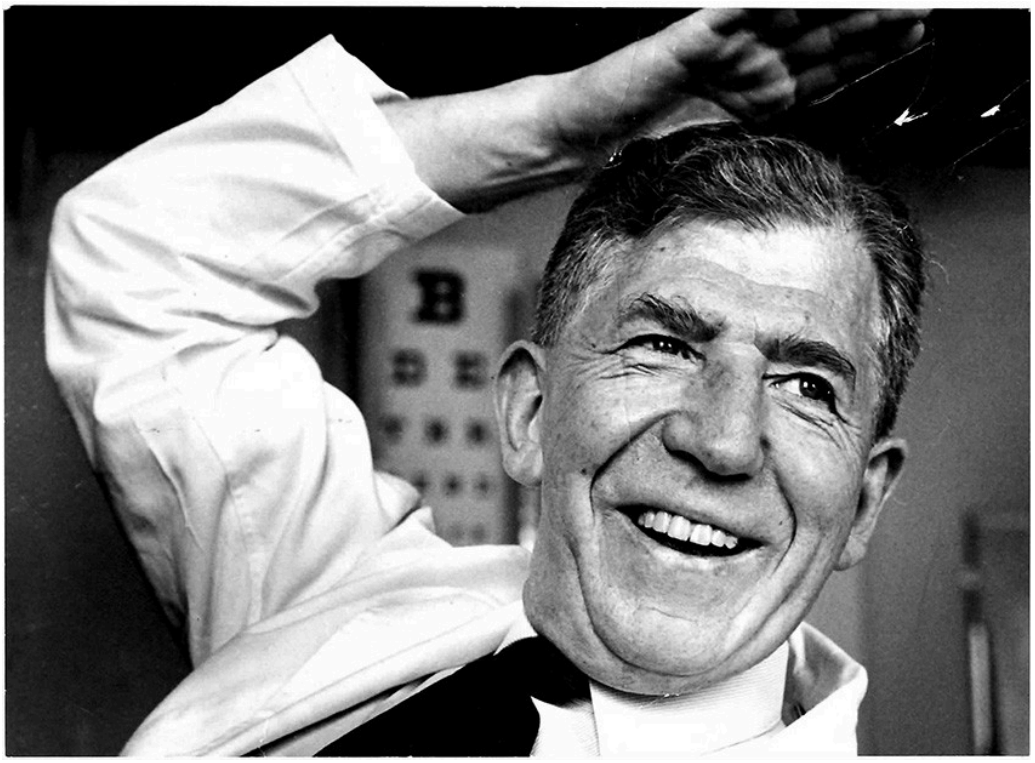

Figure 4 Marius Haarr on his 70th birthday. Photo: Sunnmørsposten

Thank you to Marius Haarr's daughters, Anne-Marie and Elisabeth Haarr, for providing biographical details and access to surviving documents and photos.

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