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HISTORICAL NOTE

Hans-Joachim Scherer (1906-1945), Pioneer in Glioma Research

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Hans-Joachim Scherer was among the most creative and productive neuropathologists of his time. Working as a political refugee in Antwerp (Belgium) during 1934-41, he published landmark papers on the morphology and biology of malignant gliomas, and was the first to clearly distinguish primary and secondary glioblastomas, and growth patterns reflecting the invasion of preexisting brain tissue (secondary structures). Scherer was a controversial personality, who at the end of World War II became entangled in the Nazi euthanasia programme.

The past decade has been characterized by an ever-increasing pace in the elucidation of the pathology and genetics of brain tumours, which has led to a decreasing half-life of cited research articles. It has become quite rare for an article to be cited more than 50 years after its publication. One exception is the work of Hans-Joachim Scherer, who in the late 1930s published some landmark studies on the pathology of glioblastoma multiforme that were far ahead of the biological thinking and comprehension of the time. His work is still quoted today, particularly with regard to recent molecular genetic studies on the evolution of human gliomas (3, 7, 17, 20, 21, 42). Here, we present a summary of Scherer's life, personality and work. More detailed accounts have been published elsewhere (19, 42).

Biography

Scherer was born on May 14, 1906 in Bromberg, Western Prussia, an area that, over the course of several centuries, had belonged either to Poland or to Germany. The Treaty of Versailles, following the first World War, decided that Bromberg would become part of the Polish state, and its current name is Bydgoszcz. Scherer's parents moved to Magdeburg in 1921. During his final two years of studying medicine in Munich, Scherer worked in the Institute of Pathology of the Schwabing city hospital with Professor Oberndorfer who was Jewish and who had to emigrate to Istanbul in 1933. Scherer published his first paper in 1929 with his fellow student Ernst Scharrer, who later became a well-known comparative neuro-anatomist (24). In 1930, Scherer published his medical dissertation on the subject of giant foldings of the gastric mucosa (25). In the same year, he started his neuropathological training with Walter Spielmeyer (10) at the German Research Institute for Psychiatry in Munich (Figure 1), with financial support from the Rockefeller Foundation. Only one year later, in July 1931, he moved to the Institute of Pathology of the University Hospital Charité in Berlin, to work with the well-known pathologist Robert Rössle. In August 1933, a few months after Hitler came to power, Scherer was arrested by the Secret Police (Gestapo), together with his colleagues Leonid Doljanski and Henry Roback. They appear to have been denounced by his landlady, because they usually spoke English during their meetings (19). After a few days, he was released but fled from Germany, first to Paris, then to Antwerp, where Ludo van Bogaert (6) offered him a position as lab chief at the Institute Bunge. In Antwerp, Scherer became scientifically very productive, and published most of his studies on the pathology and biology of human gliomas. In 1939, he took up an invitation to give lectures in the USA but failed to obtain an immigration visa; because of his birth place, he was considered Polish, and the immigration quota for Polish citizens had already been exhausted. Remaining in Belgium, even during the war, Scherer was able to publish in British and American scientific journals (36-38). In contrast to other political

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Figure 1. H.J. Scherer with his peers at the German Research Institute of Psychiatry, Munich, in 1932.

émigrés, his German passport was extended and after the invasion of Belgium by German troops, he was not arrested. Instead, he made an attempt to push Professor van Bogaert, who had given him asylum in the Institute Bunge, out of the position of Institute Director, and to assume the position himself. Following an intervention by the German neuropathologist Hugo Spatz (13), this usurpation failed. Van Bogaert dismissed Scherer who then continued his work in Ghent (Belgium) until 1941. Despite an intervention by the rector of the University of Ghent, the German military command ordered him to return to Germany, and he took up a position at the Neurological Institute in Breslau, Silesia, which is now part of Poland. In this laboratory, Scherer carried out neuropathological analyses on the central nervous system (CNS) of more than 300 Polish and German children who were euthanized in the mental hospital Loben / Lubliniecz near Breslau. Although it was very difficult to publish scientific reports around the end of the Second World War, he received permission to publish in 1944 a monograph on comparative neuropathology of mammals (39). Scherer died on April 16, 1945 in a bomb attack by the allied forces on the train station in Landshut, Bavaria, at the age of only 39 years. He was survived by his Belgian wife and a daughter.

Personality

Politically, Scherer's life appears somewhat ambiguous. Initially arrested by the Gestapo, and forced to emigrate to Belgium, he was considered an anti-fascist, but in the last years of his life he became entangled in the criminal misdeeds of the Nazi regime. The reason for his being ordered back from Belgium to Germany remains unclear and there is no documentation indicating this had any direct connection with his studies of euthanasized children in Breslau. The Nazi euthanasia programme had two major objectives. Based on its eugenic ideology, the Nazi regime pursued the elimination of all mentally disabled citizens. Mental hospitals were systematically screened and patients killed. This programme was later accelerated in order to gain hospital space for war-injured soldiers and civilians. Only in the child euthanasia programme was there also an interest in using the brains of the victims for scientific investigations. Several German neuropathologists became accomplices of this murderous program, including Hallervorden, Ostertag, Spatz and Scherer (18, 19). Participating pathologists were sworn to secrecy; it can be assumed that Scherer, too, signed such an agreement.

The episode in Antwerp also showed that Scherer was very ambitious, and his attempt to push Dr van Bogaert from his position as Director of the Institute Bunge shows that he pursued his career with some ruthlessness. He was not liked by many of his colleagues. He had the reputation of being charming and highly intelligent but he could be, on occasion, aggressive and abrasive. At the same time, his scientific contributions were regarded as outstanding by many of his contemporaries. Scherer's originality, but also his lack of communication with other scientists, is reflected by the fact that almost all of his publications were written by himself as the only author.

Scientific achievements

At his death, Scherer was only 39 years old. Over 15 years of active research, he published 39 papers, most of them original contributions. This productivity must be measured against the very difficult conditions of work both during his time as an émigré in Belgium and, particularly, after the outbreak of World War II. Methodologically, he was very careful and evaluated his observations critically.

At the beginning of his career, Scherer published some landmark papers on cerebellar degeneration and its association with a variety of sporadic and inherited neurological diseases (25-27). Another subject of investigation was neuropathological changes in animals, which culminated in his 1944 monograph on the comparative neuropathology of mammals (39). However, Scherer is best known for his contributions on tumours of the peripheral (29-31) and central nervous system.

Mesenchymal structures. His studies on the pathology and biology of gliomas start with a publication in 1933 on the significance of the mesenchymal component in brain tumours (28). In this early investigation he distinguished three types of mesenchymal structures: (*i*) the mesenchymal stroma as an inherent part of the

tumour, (*ii*) mesenchymal proliferations as a reaction to regressive tumour changes; and, (*iii*) the formation of glomeruloid vessels in malignant gliomas. The pathogenesis of microvascular proliferation remained unclear to him at this stage. He regarded it as a borderline phenomenon, which could reflect either reactive or neoplastic vessel changes.

Angiogenesis. In later studies, Scherer unequivocally concluded that microvascular proliferation is a consequence of glioma growth. He called malignant gliomas angioplastic, assuming that neighbouring foci of necrosis have an inductive effect on this process (33). He also, far ahead of his time, postulated the presence of an angiogenesis factor (angiotaxis), since he had observed that glomeruloid vascular proliferations often develop initially in peripheral infiltration zone where tumour cells are not yet discernible. He concluded that in necrotic areas, a stimulant is released by tumour tissue that induces an angioplastic effect. These observations of a very close spatial relationship between glioma growth, necrosis, and vascular proliferation are fully supported by recent studies. Scherer's carefully formulated hypothesis that ischaemic tumour cells release a factor that produces vascular proliferation has been confirmed by the finding that the gene encoding the vascular endothelial growth factor (VEGF) contains an ischaemia-responsive element (5, 41).

Primary and secondary glioblastoma. In his 1940 publication on cerebral astrocytomas, Scherer distinguished two types of glioblastomas on the basis of their mode of evolution (36). "From a biological and clinical point of view, the secondary glioblastomas developing in astrocytoma must be distinguished from primary (primary glioblastoma); they are probably responsible for most of the glioblastomas of long clinical duration." Again, this observation was ahead of the general understanding of glioma biology at this time. It was then generally believed that the glioblastoma constitutes a neoplasm of its own, and this is still reflected in the 1979 WHO classification of brain tumours in which the glioblastoma is not grouped with astrocytomas but in a separate category of embryonal and poorly differentiated neuroepithelial tumours (45). Scherer was the first to point out that gliomas may develop through two distinct pathways, *de novo* (without identifiable precursor lesion) or through progression from low-grade and anaplastic astrocytoma (36). Recent molecular studies have shown that these two subsets of glioblastomas develop through distinct genetic pathways (11, 43, 44). The primary glioblastoma typically contains an EGF receptor amplification, PTEN mutations, MDN2 amplification and P16 deletions. In contrast, the secondary glioblastoma developing from low-grade astrocytoma is typically initiated by a point mutation in the p53 tumour suppressor gene (4, 8, 14). The terms primary and secondary glioblastoma have remained conceptual and have not been introduced into the neuropathological vocabulary since histologically, they represent a common morphological endpoint. To date, no unequivocal morphological characteristics have been identified that allow a diagnostic distinction of these two sub-sets of glioblastoma (1, 2, 9).

The total length of disease is much longer in the secondary glioblastoma; however, there is no convincing evidence in support of Scherer's hypothesis that once the stage of glioblastoma has been reached, the secondary glioblastoma still has a more favourable prognosis (16).

Neuronophagia. Scherer observed that the arrangement of tumour cells around neurons is a very typical feature of diffusely infiltrating gliomas. This perineuronal satellitosis was considered by Scherer as an early sign of neoplastic infiltration and in studies on whole brain sections, he observed that nerve cells may persist for extended periods of time within a malignant glioma, and that neuronal death occurs at a rather late stage ('neuronophagique tardif') (34).

Primary and secondary structures. One of the observations for which Scherer has become best known is the identification of secondary structures. Proper (primary) structures were defined by Scherer as morphological patterns due to the intrinsic biology of tumours, which manifest independently of preexisting tissue. Examples of primary structures were rosettes, pseudorosettes, whorls and papillary structures, as well as canalicular and glandular formations. Glioma morphology was interpreted by Scherer in a dynamic way, and secondary structures accordingly defined as patterns reflecting the growth of gliomas within pre-existing brain tissue (35). Among the eight distinct types of secondary structures, sub-pial accumulations of glioma cells are perhaps the best known. They were correctly interpreted by Scherer as being the result of tumour cell migration, and the inability of glioma cells to penetrate the glia limitans and to infiltrate the subarachnoid space. He observed similar secondary structures in the subependymal region. Neuronophagia, perivascular arrangement of tumour cells, and parallel lining of tumour cells in the

cortex were also interpreted as secondary. Scherer also mentioned tertiary structures (35), although this term has never been widely used. They are defined as morphological formations resulting from the interaction of gliomas with mesenchymal cells, e.g. mesenchymal proliferation following invasion of the subaracnoid space. Scherer noted the presence of perivascular tumour cell islands (40) particularly in glioblastomas of the white-matter, and pointed out that these should be distinguished from germinal centres and from the embryonal glia operative during myelination which he had studied extensively with his colleague Roback in an earlier study (22).

Classification of gliomas. Under the influence of pathologists like Oberndorfer and Rössle, and without significant training in neurology and neurosurgery, Scherer always stressed the necessity that neuropathologists apply the principles of general tumour pathology rather than focussing on histogenesis and dysontogenetic theories (32). Accordingly, he criticized classifications largely based on the morphology of tumour cells and warned against misinterpretations of histological staining and impregnations methods.

Scherer pointed out that in his view, the diagnosis of glioblastoma must take the entire neoplasm and its architecture into consideration, and should not be based on the morphology of single tumour cells, even if the latter shows extensive anaplastic change. This was based on his interpretation of many of the glioma structures as being secondary, i.e. reflecting preexisting structures. "As the structural evolution of gliomas is an expression of the essential biological differences, this must be taken into consideration in any future classification of gliomas. The architectural development should be given the same weight as differences in localization, manner of extension, and cellular form. In future, classifications based upon cellular differences alone will not be satisfactory, especially as differences in structures in no way coincide with the cytological differences (35)." More pertinently, he stated "Pure histology is not pathology, but only one of the methods of pathology," and "Cytological or histogenetic studies in classification of gliomas cannot by themselves characterize the biology of a neoplasm (37)."

Perception of Scherer's work

The fact that Scherer's observations are still remembered and quoted today is partly due to the fact that, despite the adverse conditions during World War II, he managed to get his papers published in very prestigious English and French journals. His observations have been frequently commented upon in prominent neuropathological textbooks (1, 2, 12, 15, 46). Lucien Rubinstein stated: "The contributions of Scherer on the patterns of growth and spread of gliomas, particularly the cerebral astrocytomas, are of crucial importance for the understanding of the process of expansion and infiltration in these neoplasms, and have shed considerable light on the relationship that exists between the morphological features of the diffuse tumours and the environmental influences determined by the host (23)." Today, the knowledge of secondary structures in malignant gliomas is still a key factor in the histopathological classification of these neoplasms. Scherer's concept of primary and secondary glioblastomas opened a new approach to the understanding of distinct genetic pathways leading to the glioblastomas as the common morphological endpoint.

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