History of the Letzte Wiese/Last Meadow Concept of Brain Ischemia

Konstantin-Alexander Hossmann, MD, PhD; Wolf-Dieter Heiss, MD

In the history of stroke research the term letzte Wiese (English last meadow or last field) was introduced in the early fifties of the past century to describe the risk of low blood perfusion in the periphery of a vascular territory. The term appears 1952 in the discussion of a colloquium held by the German Society of Physiological Chemistry in the small city Mosbach, located close to the scenic river Neckar in the north of the federal state Baden-Württemberg.1 The symposium entitled Chemie und Stoffwechsel des Nervengewebes (chemistry and metabolism of nervous tissue) comprised 5 presentations on various aspects of brain function and metabolism. One of these was given by Erich Opitz, Chair of the Physiological Institute of the University Kiel. In his presentation Energieumsatz des Gehirns in situ unter aero- ben und anaeroben Bedingungen (energy metabolism of the brain under aerobic and anaerobic conditions), he addressed the magnitude of metabolic activity required to maintain the structural integrity of the brain (Strukturumsatz). In the discussion after his presentation, Max Schneider, Chair of the Physiological Institute of the University of Cologne, remarked that a differentiation between structural and functional activity of the brain can be obtained by gradually reducing the blood perfusion of an isolated head preparation and recording the suppression and recovery of the electroencephalogram. The lowest flow rate down to which spontaneous electroencephalogram activity persists is the amount required to maintain functional activity, and the lowest flow rate which is tolerated for some time without causing irreversible suppression of the electroencephalogram corresponds to the amount required to preserve structural integrity. This approach anticipated the latter differentiation between core and penumbrar of evolving brain infarction introduced by Astrup et al2 after occlusion of the middle cerebral artery. However, as pointed out by Schneider,3 global measurements of blood flow in the isolated head preparation preclude precise evaluations of cortical blood flow because at declining blood supply the basal parts of the brain are better perfused than the cortex, similar to the situation of reduced water supply to a stretch of irrigated meadows where die letzten Wiesen schlechter gestellt sind als die erste (the last meadows are worse off than the first one). The term letzte Wiese, therefore, was initially introduced to describe a methodological problem rather than a new pathophysiological concept.

This quickly changed. In a review article on cerebral blood flow (CBF) and oxygen supply published shortly later, Schneider used again the term letzte Wiese to explain that this principle could be of importance for the topography of ischemic lesions. To stress his argument, he referred to a publication from his laboratory where intravenous dye injections were performed to test the permeability of the blood–brain barrier after brain anoxia.4 To facilitate the detection of dye extravasations, the stained blood was rinsed from the vasculature after sacrifice by intracarotid infusion of saline. It turned out that with this procedure, a semicircular strip of cerebral cortex covering parts of gyrus sigmoides posterior, gyrus lateralis, and gyrus postlateralis remained intensely stained—not only in anoxic but also in normoxic control animals—and that the staining was caused by aggregation of dye particles in vessels in which the blood was not properly washed out. The topical pattern of washout failure resembled the previously described histopathological pattern of brain injury after transient experimental occlusion of the pulmonary artery,5 as well as the pattern of granular atrophy in the cerebral form of von Winicrter–Buerger’s disease,6 both of which localized to the border zones between the supplying territories of the anterior, middle, and posterior cerebral arteries. The authors, therefore, cautiously raised the question, whether this similarity might be mehr als eine äußere (more than apparent).4

It was not until 1959, however, that the German neurosurgeon Wilhelm Tönnis together with his assistant Wolfgang Schiefer associated this pattern more affirmatively with the vascular anatomy of the brain and explicitly gave credit to Schneider’s concept of letzte Wiese to explain the manifestation of circulatory disturbances in the border zones between the 3 large brain arteries, as well as in basal ganglia and internal capsule.7

This annotation went well beyond Schneider’s early remarks and firmly established the concept of letzte Wiese for the classification and pathophysiologial interpretation of a subgroup of brain infaracts. In fact, the neurologist and neuropathologist Klaus Joachim Zülch, a former collaborator of Wilhelm Tönnis, undertook the ambitious task to document...
the clinical and pathomorphological heterogeneity of brain infarcts and to correlate the various stroke patterns with the underlying vascular pathology. On the basis of >700 brain autopsies obtained from patients with cerebrovascular disease, as well as on the thorough analysis of previously reported morphological data, he differentiated between single and multiple infarcts developing within or between the supplying territories of the large brain vessels. According to the letzte Wiese concept, he suggested that infarcts in the most distant supply areas of a gradually obstructed neck or brain artery could be triggered off by a drop of blood pressure, even within the physiological range of circadian blood pressure variations.

This highly quoted hypothesis had a profound influence on stroke research. Letzte Wiese zones and the associated interterritorial infarcts have subsequently been referred to as frontier, frontier-line, distal field, watershed, boundary, border-zone, borderline, borderland, endzone, junctional, and terminal zone infarcts, respectively. Letzte Wiese phenomena have also been reported in many other parts of the body, including retina, spinal cord, heart, liver, limbs, bone articulations, and even teeth.

During the early history of stroke research, the letzte Wiese phenomenon has been explained by a simple unified theory of focal vascular obstruction in combination with general hemodynamic insufficiency. With more detailed information about the pathogenesis of letzte Wiese–associated insults, alternative explanations have been established, which include microembolism, vasospasm, hemorheological, and even metabolic disturbances. In the following, an attempt will be made to discuss the characteristics of letzte Wiese and the associated circulatory disturbances in the light of current pathophysiological knowledge.

**Localization of Letzte Wiese**

According to the original concept, letzte Wiese is the most distant field of the supply territory of an artery. On the surface of the brain, these fields are located at the borders of the 3 main arterial territories, that is, those of the anterior, middle, and posterior cerebral arteries (Figure). Viewed from the lateral side, these borders form a parasagittal, semicircular strip, which stretches from the frontal to the temporal lobe. Within this strip, the temporoparietal gyrus angularis is of particular pathophysiological importance because this area is the boundary between the 3 cerebral arteries (Dreiländereck) (Figure). Viewed from the lateral side, these borders form a parasagittal, semicircular strip, which stretches from the frontal to the temporal lobe.

In the depth of the brain, letzte Wiese zones are located between putamen and insula at the border of the deep and superficial branches of the middle cerebral artery, and at the terminal fields of various end arteries which do not make anastomotic contact with other vascular territories. These are the basal ganglia, supplied by the lenticulostriate arteries, the periventricular white matter substance supplied by the long penetrating arteries and the hippocampal formation, which receives its blood supply mainly from endarterial branches of the anterior choroidal and posterior cerebral arteries.

Letzte Wiese zones in the cerebellum are located at the borders between the supply territories of the anterior inferior, superior, and posterior inferior cerebellar arteries and in the spinal cord at the midthoracic level between the supply territories of the segmental artery VI which originates from vertebral artery, and the segmental artery IX which is a branch of the aorta. Topically defined letzte Wiese zones have also been detected at various levels of the medullar–pontine–mesencephalic axis after vertebral artery occlusion, but these findings are inconsistent and probably of lesser pathophysiological importance.

**Pathophysiology of Letzte Wiese**

In the healthy brain, powerful regulatory systems control the adequate and even supply of blood and oxygen to all parts of all vascular territories, including the most distant letzte Wiese zones. Differences in local perfusion pressure are compensated by myogenic adjustments of local vascular resistance (autoregulation), and variations in local oxygen supply or metabolic activity are coupled to appropriate variations of local blood flow by a complex system of chemical and neurogenic influences that adjust vascular resistance to the oxygen requirements of the tissue (neurovascular coupling). This highly controlled system is basically different from the passive flow dynamics of agricultural irrigation where the water supply steadily declines with increasing distance from the origin of the irrigation channel.

Another major difference is the abundance of Anastomotic connections between neck and brain arteries. The 4 neck arteries—2 carotid and 2 vertebral arteries—are interconnected at the base of the skull by the circle of Willis from where the 6 main cerebral arteries originate: 2 anterior, middle, and posterior cerebral arteries. Within the brain, the distal cortical branches of the cerebral arteries which supply the letzte Wiese zones are interconnected by the network of Heubner’s pial anastomoses. If the blood flow in any of the 6 cerebral arteries is reduced, orthograde flow to the letzte Wiese zones may be impaired, but as the decline is compensated by retrograde collateral blood supply from the adjacent vascular territories, the letzte Wiese zones are actually protected against ischemic
injury. The flow reversal in the periphery of the supply territory of an obstructed artery is the basis of the penumbra phenomenon, which states that in focal ischemia the central most severely damaged core is surrounded by the less severely injured, potentially viable, penumbra. The risk of hypoperfusion in letzte Wiese zones arises mainly in vascular territories supplied by endarteries, or—for anastomotically connected arterial territories—when blood supply to the adjacent territories is also reduced. Such a situation may arise from systemic hypotension, vascular occlusions proximal to the circle of Willis (notably the internal carotid artery), multiple intracerebral vascular obstructions, generalized vasospasms, reduction of blood fluidity, microembolism, or any combination of these.

On the basis of these general considerations, the specific nosology of letzte Wiese–associated brain lesions will be briefly reviewed.

**Clinical Manifestations of Letzte Wiese Winiewarter–Buerger’s Disease**

The concept of the letzte Wiese was initially derived from the topographical similarity between the anatomy of cortical border zones and the pathomorphological pattern of the cerebral form of Winiewarter–Buerger’s thrombangiitis obliterans. A closer look at the original publications reveals that this similarity refers only to 1 subtype of the disease, which is characterized by the generalized—possibly vasospastic—involve ment of the most distant ramifications of all brain arteries including the striolenticular and cerebellar arteries. In this subtype, vascular occlusions colocalize with the semi-circular strip of granular atrophy along the cortical border zones, which points to distal local effects rather than to proximal vascular occlusion in combination with a reduction of global blood supply, as postulated by the letzte Wiese concept. However, Miller Fisher later reported a similar morphological pattern after proximal vascular occlusion and concluded that the distal alterations were because of secondary peripheral blood stagnation, followed by thrombotic obliteration of vessels (stagnation thrombosis). Recently, blood hypercoagulability has been observed in connection with the disease that would be in support of a multifactorial pathogenesis. Whatever the prevalent pathogenesis may be, the incidence of cerebral thrombangiitis obliterans when compared with other ischemic events is low. The clinical interest of the disease is, therefore, much lower than its historical importance for the letzte Wiese concept may suggest.

**Stroke**

The most frequent association of brain lesions within the areas designated as letzte Wiesen is acute ischemic stroke. Inner and outer boundary zone infarcts have been repeatedly described and are generally accepted terms in all stroke classifications. The incidence of such infarcts when compared with other stroke subtypes, however, is rather low. In contrary, in the vast majority of ischemic infarcts, cortical letzte Wiese zones representing the outer border of the vascular territory are more resistant because of the collateral blood supply from the adjacent territories. In a series of 400 cerebral infarcts studied in consecutive autopsies, only 37 (9.3%) were located in border zone areas when compared with 363 (90.7%) in other locations. More recent estimates based on neuroimaging data come up to similar conclusions. Clinical symptoms include the man-in-the-barrel-syndrome described by Mohr where ischemic lesions in the high convexity anterior border zones result in a syndrome biased toward brachial paralysis. Because the patients are able to move the face and legs, they give the appearance of having the upper body constrained within a barrel.

**Global Ischemia**

Global interruption of CBF as induced by severe cardiocirculatory failure or cardiac arrest results in greatly differing pathomorphological lesions, depending not only on the duration and severity of ischemia but also on the quality of reperfusion. Here, posts ischemic hypoperfusion and the associated impairment of neurovascular coupling seems to be of particular relevance because the potential mismatch between metabolic activity and blood flow elicits the risk of relative hypoxia first in the letzte Wiese areas in which blood perfusion pressure is lowest. This explains the occasional evolution of border zone lesions after complete circulatory arrest, as documented already in the early literature on global ischemia. In our laboratory, prolonged interruption of blood flow in the primate brain also resulted in sharply demarcated outer and inner border zone lesions despite unambiguous evidence of functional and biochemical recovery in most other parts of the brain.

In this context, the well-known phenomenon of selective vulnerability of hippocampal CA 1 sector after brief periods of global ischemia is of historical interest because it evoked a sharp scientific dispute between 2 prominent neuroscientists: Oskar Vogt and Walter Spielmeyer. Spielmeyer explained the ensuing hippocampal sclerosis with a reduced blood perfusion because the hippocampal vessels are end-arteries, whereas Vogt attributed the lesion to molecular pathoclitic properties of the vulnerable neurons. Today, the molecular pathogenesis of selective vulnerability is generally accepted. However, a vascular contribution cannot be dismissed because stereological counts of perfused capillaries revealed misery-perfusion in those areas which have most intense injury.

**Microembolism**

The possibility that letzte Wiese lesions might be induced by multiple showers of microemboli or cholesterol crystals from either the heart or the carotid arteries has been raised early, but only the combination of careful clinical analysis with advanced neuroimaging methods provided solid evidence in support of this pathology. Microembolisms are mainly associated with cortical border zone infarcts, whereas inner border zone lesions are mainly caused by hemodynamic compromise. Microembolism is probably also involved in the pathophysiology of the not so rare border zone lesions after cardiac surgery and extracorporeal circulation. Interestingly, persistence of microembolic occlusions in the peripheral branches of brain arteries replicates the experimental dye washout failure alluded to by Schneider and points to the importance of an
adequate local blood perfusion pressure to clear microembolic particles from the brain vasculature.

**Neuroimaging**

According to the letzte Wiese concept, the susceptibility of the watershed areas for ischemic lesions is thought to result from low blood perfusion pressure in the final arterial distribution, especially in patients with large artery occlusion or stenosis. Therefore, regional flow measurements can detect these areas and assess the threat to develop damage. Regional CBF measurements with intracarotid injection of Xenon 133 were able to document the critical reduction in perfusion in the cortical watershed (CWS) areas in patients with obstructive neck vessel disease; they also indicated the potential of aggravation of the critical blood flow by intracerebral steal phenomenon induced by vasodilatation in unaffected arteries with limited blood supply caused by arterial obstruction and the development of infarction in the further course. Misery perfusion as characterized by the mismatch between critically reduced flow and sufficient oxygen supply (measured by the increase in oxygen extraction fraction) was observed in the parieto-occipital watershed area by positron emission tomography, and its reversal was documented after extra-intracranial arterial bypass surgery. Since then the pathophysiology of watershed infarction was studied repeatedly mainly by positron emission tomography, but hemodynamic compromise in the border zones was also evident in diffusion- and perfusion-weighted magnetic resonance imaging and in CBF studies by single photon emission tomography under acetazolamide challenge.

The risk for recurrent stroke in patients with major cerebral arterial occlusive disease is especially increased when oxygen extraction fraction was increased in the watershed region, but selective neuronal damage may occur beyond the border zone infarctions within the areas of hemodynamic compromise. The hemodynamic impairment caused by occlusive large vessel disease (stage I: decline of perfusion pressure and autoregulatory vasodilatation; stage II: decrease of CBF and increase of oxygen extraction fraction) can also be tested by single photon emission tomography with hypercapnia or intravenously administered acetazolamide to assess the risk of watershed infarctions.

Two types of watershed infarctions can be distinguished: CWS between the cortical territories of the anterior, middle, and posterior cerebral arteries, and internal watershed (IWS) in the white matter along and slightly above the lateral ventricle, between the deep and the superficial systems of the anterior and middle cerebral arteries. Most of the CBF studies agree that the IWS is more sensitive to hemodynamic failure than CWS, and IWS infarcts—especially the rosary-like pattern—are related to hemodynamic impairment. Small infarcts in the centrum semiovale may predict impending cortical stroke. The hemodynamic compromise leading to infarctions in the centrum semiovale was also expressed in metabolic changes in magnetic resonance spectroscopy, which were correlated to decreases in regional oxygen extraction fraction. The development of small infarcts within the IWS could be followed also by diffusion-weighted magnetic resonance imaging.

Patients with IWS infarcts had higher degrees of occlusive vascular disease and showed more severe early and late clinical course than those with CWS infarcts. Only a few studies found some hints for additional embolic events within the hemodynamically compromised IWS.

For infarcts within the CWS, hemodynamic mechanisms are more frequent in the anterior than in the posterior watershed. However, growing evidence suggests that artery-to-artery embolism coexists with hypoperfusion, and that stagnant flow increases the risk of embolic events, facilitating the development of infarcts in the CWS when small emboli lodge in the letzte Wiesen. Several studies reported complete or partial resolution of previously observed perfusion abnormalities after successful revascularization surgery.

**Conclusions**

The letzte Wiese concept of hemodynamic failure in the most distant field of an arterial supply territory was developed in the early fifties of the last century and represents one of the first attempts to understand the topography of human cerebral infarcts on the basis of animal experimental pathophysiology. Today, it is clear that ischemic infarcts in letzte Wiese zones are rare, and that in most instances of cerebrovascular disease, the collateral system of the brain tends to protect rather than to damage the distant fields of an occluded artery. The historical importance of the letzte Wiese concept, therefore, is not the elucidation of a prevalent pathogenetic principle of infarct evolution but the beginning of an experimentally guided stroke research. Looking at the deficits of translational stroke research, this development is still in its infancy. The history of letzte Wiese may serve as a guide for further progress in the field.

**Disclosures**

None.

**References**


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