FISCHER'S MATRIX

The 1907–1912 Neuropathology of Oskar Fischer as Founder Document of the Seventh Convergence Axis on Extracellular Matrix and Perineuronal Net Integrity in Alzheimer's Disease

A Companion Synthesis to the Convergent Synaptic Collapse and Homeostatic Microglial Collapse Theses

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Abstract

The seventh convergence axis emerging from the Oskar Fischer Prize corpus is organized around the integrity of the cortical extracellular matrix and in particular the perineuronal net sheaths of parvalbumin-positive interneurons, whose disruption by matrix metalloproteinase-9, ADAMTS-4, cathepsin-S, and the broader microglial effector repertoire has been identified in the companion Homeostatic Microglial Collapse thesis as the substrate at which microglial attack and microglial failure become mechanistically indistinguishable. The axis is supported by a five-researcher clique in the contemporary literature including Crapser, de Vries, Carulli, Fawcett, and van 't Spijker, and it occupies a position transverse to the six convergence nodes previously identified in the Convergent Synaptic Collapse synthesis. This paper argues that the extracellular-matrix framing of Alzheimer's disease pathology is not in fact a twenty-first century discovery of the perineuronal net literature but a direct rediscovery of the founding neuropathological framework developed by Oskar Fischer in his 1907 *Monatsschrift für Psychiatrie und Neurologie* paper on miliary necrosis with nodular proliferation of the neurofibrils, his 1910 *Zeitschrift für die gesamte Neurologie und Psychiatrie* monograph on presbyophrenic dementia, and his 1912 follow-up in the same journal. We show that Fischer's descriptive language, his staining methodology, his stage classification of the lesion, his cortical-layer distribution data, and his explicit rejection of glial, neuronal, bacterial, and plasma-derived interpretations of the plaque all together constitute a fully formed matrisomal theory of Alzheimer's disease pathogenesis a century before the molecular tools required to validate it became available. In particular, we show that Fischer's 1910 eight-stage remodeling sequence — from the initial "star formation" through "morning star," "spoke," "wheel," "fibrous ball," "fur-like destruction of the vascular wall," "destruction of the drusen," and finally "diffuse infiltration of the nervous tissue" — is most accurately read as the first systematic histological description of progressive extracellular matrix remodeling in the Alzheimer's disease cortex, and that Fischer's preferred terminology of *Sphaerotrichia cerebri multiplex* ("multiple spherical hair-formations of the brain") captures the matrisomal character of the lesion more precisely than the subsequent twentieth-century language of amyloid plaques. We argue that four specific convergences link Fischer's primary observations to the modern perineuronal net literature: first, Fischer's description of the plaque halo as a densification of the cortical ground substance rather than a foreign deposit; second, his eight-stage sequence as a century-early description of matrix metalloproteinase-driven remodeling; third, his frontal and upper-cortical-layer distribution data as a direct anatomical match to the layers and regions in which perineuronal nets around

parvalbumin-positive interneurons are most densely concentrated; and fourth, his clubbed claviform neurite formations as the dystrophic process withdrawal now understood to follow perineuronal net loss. We argue further that the subsequent century of Alzheimer's disease research has been shaped by the adoption of Alzheimer's intracellular neurofibrillary framing in preference to Fischer's extracellular matrix framing, and that the emergence of the seventh convergence axis represents the rediscovery of the founder document after a century of displacement. The practical consequence is that the Oskar Fischer Prize, named for the man whose original observations have been rediscovered rather than superseded, should be understood as honoring the researcher whose framing the field is only now returning to, and the perineuronal net axis should be understood not as a novel seventh node but as the restoration of the original founder description.

1. The Forgotten Framing

The Oskar Fischer Prize is named for a neuropathologist whose work, despite being published in the same year as Alois Alzheimer's Auguste D. case and on a substantially larger cohort of sixteen senile dementia patients, was systematically marginalized throughout the twentieth century. The reasons for this marginalization are partly biographical — Fischer was Jewish, worked in Prague rather than Munich, lacked the institutional support network that Alzheimer enjoyed through his relationship with Kraepelin, and was ultimately arrested by the Gestapo in 1941 and died in Theresienstadt concentration camp in 1942 — and partly conceptual, having to do with the particular framing of the plaque lesion that Fischer chose and that the field subsequently rejected in favor of Alzheimer's alternative framing. This paper is concerned with the conceptual story rather than the biographical one, and it argues that the framing Fischer chose has been rediscovered rather than superseded, and that the perineuronal net literature emerging in the early twenty-first century is most accurately read as a return to Fischer's founder description after a century of displacement.

The central conceptual claim of the paper is simple but consequential: Fischer, in his 1907 *Monatsschrift für Psychiatrie und Neurologie* paper, his 1910 *Zeitschrift für die gesamte Neurologie und Psychiatrie* monograph, and his 1912 follow-up paper in the same journal, developed a fully formed extracellular-matrix theory of the Alzheimer's disease plaque lesion. He characterized the plaque as a remodeling of the cortical ground substance rather than as a deposit of foreign material, as a progressive matrix phenomenon following a discrete eight-stage sequence rather than as a static end-stage lesion, as a cortical-layer-specific process with sharp regional preferences, and as the anatomical substrate of a specific clinical syndrome — presbyophrenic dementia with confabulation and hallucination — whose circuit-level basis we now understand to depend on the parvalbumin-positive interneuron populations most heavily ensheathed by perineuronal nets. Every one of these claims is present in Fischer's primary texts, supported by detailed histological observation, and stated in terms that would be unremarkable if they appeared in a 2024 *EBioMedicine* paper rather than in a 1910 German neuropathological monograph.

The paper proceeds in four stages. First, we undertake a close reading of Fischer's 1907, 1910, and 1912 papers, drawing on the available English translations of the primary texts, with particular attention to the specific descriptive language Fischer uses for the plaque lesion and to the methodological care with which he distinguishes his observations from the competing glial, neuronal, and bacterial interpretations circulating in the period. Second, we summarize the modern perineuronal net literature with sufficient specificity to make the comparison tractable. Third, we identify four specific convergences between Fischer's primary observations and the modern PNN axis, arguing in each case that the convergence is not a matter of general resemblance but of precise descriptive and anatomical correspondence. Fourth,

we consider the conceptual cost of the path not taken — the extent to which the twentieth-century marginalization of Fischer's framing shaped the intellectual development of the field in ways that have only recently begun to be corrected — and we argue that the perineuronal net axis, far from being a seventh node to be added to the six previously identified in the Convergent Synaptic Collapse synthesis, is better understood as the restoration of the founder description from which the six modern nodes have been, in effect, derivations.

2. Fischer 1907: The Birth of the Matrix Lesion

Fischer's founding paper, *Miliare Nekrosen mit drusigen Wucherungen der Neurofibrillen, eine regelmässige Veränderung der Hirnrinde bei seniler Demenz* — "Miliary necroses with nodular proliferations of the neurofibrils, a regular alteration of the cerebral cortex in senile dementia" — was published in volume 22 of the *Monatsschrift für Psychiatrie und Neurologie* in 1907, based on a cohort of sixteen senile dementia cases, and built explicitly on the earlier work of Redlich, who had described similar lesions in two cases in 1898 but had interpreted them as proliferated glial cells that had replaced necrotic neurons. Fischer's paper is, structurally, a refutation of Redlich's interpretation and a proposal of a new framework, and the new framework is the matrix framing that the modern PNN literature has rediscovered.

Fischer's methodology is important to the argument. He examined his sixteen cases using a combination of staining methods — hematoxylin-eosin, van Gieson, polychrome methylene blue, Weigert's myelin stain, Weigert's glial stain, Scarpatetti's method, his own glial coloration protocol, tannin-methylene blue, and the Bielschowsky silver method — and the systematic comparison across stains is what allows him to draw his conclusions about the matrix character of the lesion. In particular, he reports that the plaque lesion is visible with hematoxylin-eosin and van Gieson but "with the stain by Van Gieson, the plaques show a characteristic structure that differs with their size." The smallest foci "have a homogeneous aspect which is reminiscent of necrosis with signs of granulation and they are easily distinguished from the surrounding tissue." The larger lesions, viewed under oil immersion, consist of "predominantly of opaque clots; to a lesser extent it appears as a very dense structure with radial filaments; in the latter case, furthermore, the rim is not exactly circular but finely indented and notched, but still clearly distinguishable from its surroundings."

The phrase "very dense structure with radial filaments" is the first important observation. Fischer is describing, in 1907, a structure with a fibrillar radial organization around a denser center — the exact morphology that modern matrisomal histology recognizes as a disturbance of the extracellular fibrous network. He continues: "The next-larger plaques have a central part, structurally similar to the previously described plaques, which are connected with a ring-shaped halo of a 15–25 μ diameter. The central part is of a granular and clot-like nature, and stains opaque-bluish colour with hematoxylin and eosin. Between the clots it is possible to observe a bluish coloured filamentous mass which is often arranged radially and which sometimes shows very small spines, only observable with oil immersion." The distinction Fischer draws between the central clot and the radial filamentous halo is not a merely descriptive one: he treats it as evidence that the plaque has an internal structure consisting of distinct components with different staining properties, and he uses this internal structure as the basis for his subsequent argument that the lesion is a matrix process rather than a glial one.

The critical passage in the 1907 paper is the following, which deserves to be quoted at length: "The surrounding halos have the same structure as the remaining ground substance of the cortex, but with the difference that they are arranged somewhat more closely. The next-largest plaques whose size is often

from 60 to 80 μ, more rarely from 100 to 120 μ, have nearly always an appearance which is easily reminiscent of an *Actinomyces* nodule. With hematoxylin stain, the centre consists of different shades of opaque-bluish coloured clots, in which oil immersion often shows a tangled network of rigid, dark-coloured vessels, which have a certain resemblance to fibrin or *Streptotriches*. Around the ring, the tissue is more brightly coloured with a filamentous structure and an obvious radial disposition. Often, delicate greyish-blue coloured, claviform structures are found disposed radially; the edges stand out quite clearly from their surroundings; at times, however, a gradual transition can be observed."

Four features of this passage are worth drawing out, because each of them anticipates a specific feature of the modern perineuronal net lesion. First, Fischer explicitly describes the halo as "the same structure as the remaining ground substance of the cortex" — that is, as a modification of the cortical extracellular matrix rather than as a foreign deposit. The halo is not made of a new material; it is the existing matrix, rearranged. Second, he describes the halo as "arranged somewhat more closely" — a densification of the matrix, the opposite of the diffuse spreading one would expect from a leaked plasma component or a diffused toxin. Third, he invokes the simile of the *Actinomyces* nodule and the *Streptotriches* genus (now *Streptothrix*) — filamentous microorganisms whose characteristic gross morphology is precisely a radially organized matrix structure around a dense core. Fischer chose these similes because they captured the radial matrix organization he observed, and not, as the later spirochete-hypothesis literature incorrectly inferred, because he believed the lesion was of bacterial origin. Fourth, he describes the claviform structures — the clubbed, rounded formations — as disposed radially at the edges, with edges that "stand out quite clearly" from their surroundings: these are what the modern literature would call dystrophic neurites, and their radial disposition at the lesion periphery is a feature Fischer treats as one of the most consistent properties of the plaque.

Fischer explicitly rules out the competing interpretations of the lesion available in the 1907 literature. On Redlich's glial proliferation hypothesis, he writes: "Redlich's view is based on the aspect of the small focus with the usual methods of eosin and van Gieson in which the focus appears as a simple thickening of the basic tissue of the cerebral cortex. With careful observation it shows a very fine radial structure, yet with these stains the appearance of the dense fine-filamentous neuroglia (Redlich made a striking comparison between the appearance of the neuroglia and simple thread) is so different (as Redlich himself admitted) that a transformation to the usual spider's web cannot be conceived without difficulties. Redlich failed to stain the glia. In my successful glia preparations I did not find any glia fibres or proliferated glia cells in or around the plaques." On the bacterial hypothesis, he writes: "In preparations of the myelin sheath, with the Weigert method, the plaques are often completely myelin-free, and appear as yellow globules, of which especially the largest, clearly push aside the nerve fibres. Vertical and horizontal vessels arch around the plaques. Because of the apparent granular-necrotic, often filamentous structure, and the club-like formations, which very much resembled a glandular actinomycosis, a wide variety of bacterial stains were used. Also the methods of Gram and Ziehl-Neelson were tried, but with completely negative results; the foci remained unstained."

Fischer's rejection of the bacterial hypothesis is particularly important because it has often been misread, both in his own period and in subsequent historiography, as a tentative acknowledgment that the lesion might be bacterial in origin. The actual passage is definitive: all of the standard bacterial stains available in 1907 — Gram, Ziehl-Neelsen, the various methylene blue protocols, and the Weigert methods — produced negative results, and Fischer explicitly uses this to reject the bacterial interpretation. He invokes the *Actinomyces* and *Streptotriches* comparisons as morphological similes only, as analogies to the radial matrix organization he observes, and not as proposed etiological agents. The subsequent twentieth-century literature that positions Fischer as a precursor to the microbial hypothesis of

Alzheimer's disease rests on a misreading of these passages.

Having ruled out the glial and bacterial interpretations, Fischer then states his positive framework: "It was more reasonable to consider it as a peculiar type of necrosis, although noting that a degradation of nervous elements, cells or fibrils, at least in the smallest of the foci, was not demonstrable. However, necrosis might be the most appropriate description, since the ulterior aspect reminds one above all of the necrotic process. During the enlargement of the plaques, the fibrils spread out more and more and those that are closest show particular symptoms of proliferation, in the form of spindle-shaped thickenings, and rounded, club-like, multiply ramified sproutings which are arranged preferentially on the edge of the plaques in a radial disposition with a thickened end toward the outside, so that the pattern resembles very much an actinomycotic gland. Therefore the entire plaque is nothing else than a, not precisely definable, necrosis reminiscent of extraneous deposition with proliferative changes in the nerve fibres." And then, at the end of the paper, he offers the term that would become his preferred designation for the lesion in subsequent work: "glandular necroses, as I wish to label them, in brief" — the German *drüsige Nekrose*, which in Fischer's usage captures both the radial gland-like morphology and the necrotic character of the central core.

The clinical correlation Fischer reports is equally important for the connection to the modern perineuronal net axis. He writes: "A summing up of the clinical symptoms of all the cases led us to the surprising result, that the cases without necrosis were simple senile dementias with a simple decrease of the psychological and intellectual capacities, while the others were more or less evident presbyophrenias with confabulations and more serious memory disorders. Exactly those cases that showed glandular necroses in an enormously abundant number were clinically characterized by a very rapid development of the disease and especially by frequent hallucinations." And in his summary: "In senile dementia there occur very peculiar claviform proliferations in the neurofibrils, which, in this form, have so far been unknown in the brain; In 'glandular necrosis' we find the most important anatomical substrate of presbyophrenia."

The clinical syndrome Fischer identified as the matching substrate for his lesion — presbyophrenia, characterized by confabulation, hallucination, and rapid memory loss — is the same syndrome whose circuit-level substrate the modern literature has since traced to the parvalbumin-positive interneuron populations of the hippocampus and entorhinal cortex, whose perineuronal net integrity determines their capacity to sustain theta and gamma oscillations critical for episodic memory encoding and confabulation-gating. Fischer identified the clinical phenotype, identified the anatomical lesion, identified the cortical localization, and identified the matrix character of the lesion — and he did all of this in a thirteen-page paper published in 1907.

3. Fischer 1910: Sphaerotrichia Cerebri Multiplex and the Eight-Stage Remodeling Sequence

The 1907 paper was a "provisional communication," and Fischer treated it as a first statement of findings that required more extensive material and more systematic treatment. His 1910 monograph in volume 3 of the *Zeitschrift für die gesamte Neurologie und Psychiatrie — Die presbyophrene Demenz, deren anatomische Grundlage und klinische Abgrenzung* ("Presbyophrenic dementia, its anatomical basis and clinical definition") — is the extended treatment, running to over one hundred pages and covering fifty-eight brains in which Fischer identified the lesion, against a control group of normal aged brains in which he did not. The 1910 monograph is the single most important primary document in the Fischer corpus and is the founder document of the matrix framing of Alzheimer's disease pathology.

Fischer opens the monograph with a statement of methodology: "The change in the brain under consideration can best be represented by the method of Bielschowsky. With most of the usual and histological staining methods in use up to now, the elements in question are not colored at all or are so little distinct that they can very easily be overlooked; This is also the reason why this frequent change only became known so late." The methodological point matters because it explains why Fischer's lesion was invisible to the field until the Bielschowsky silver impregnation technique became available: the lesion was an extracellular matrix phenomenon, and extracellular matrix components are precisely the elements that hematoxylin-eosin, Nissl, and conventional cellular stains fail to visualize. The Bielschowsky method, because it impregnates fibrillar proteins of the extracellular compartment along with axonal neurofibrils, was the first method capable of rendering Fischer's lesion visible, and the history of the field's late recognition of the plaque is the history of a matrix lesion awaiting a matrix-visualizing stain.

Fischer then proposes a new name for the lesion: *Sphaerotrichia cerebri multiplex*, which he glosses as "an expression that should not indicate anything other than that it is a matter of a mostly spherical formation of threads." The Greek roots are *sphaira* (sphere) and *thrix* / *trichia* (hair, thread), and Fischer's preferred term means, literally, "multiple spherical thread-formations of the brain." The terminology is significant because it captures exactly the matrisomal character of the lesion that Fischer had identified in 1907 and was now elaborating: the lesion is a three-dimensional, spherical, thread-based formation in the brain parenchyma, and its essence is the fibrillar matrix organization rather than any particular chemical composition. The fact that this terminology was not adopted by the subsequent literature — which preferred the term "senile plaque," and later "amyloid plaque" after Divry's 1927 identification of the amyloid character of the central core — is itself a marker of the conceptual path the field took: the "plaque" terminology emphasized the deposit character of the lesion and shifted attention from the matrix organization to the chemical identity of the central core, while the "Sphaerotrichia" terminology emphasized the matrix organization and would have preserved the matrisomal framing if it had been adopted.

The most important scientific content of the 1910 monograph is the staging classification. Fischer, on the basis of his fifty-eight-brain cohort, identified eight distinct morphological stages of the Sphaerotrichia lesion, and he argued — with an explicit methodological caveat about the difficulty of establishing temporal sequence from cross-sectional post-mortem material — that these stages represent a progressive developmental sequence of the lesion from its initial appearance through its terminal destruction of the surrounding tissue. The stages, in Fischer's own terms, are:

1. **Stage of star formation** — "the smallest of the observed forms is drawn... at this stage represent themselves as irregular stars" of two-micron fibrillar elements.

2. **Stage of morning star formation** — "the larger drusen have morning star shapes in different sizes... They differ from the asterisk form in that they are larger throughout and the threads are regularly set radially."

3. **Stage of spoke formation** — "a very common formation is shown... you can see the stretches here radiant and rather massive growing out of the morning star — if I may say so. At this stage the tissue retracts and a halo develops."

4. **Stage of wheel formation** — formation with a peripheral halo and radial spokes linking center to margin.

5. **Stage of the fibrous ball** — the classic mature plaque, in which "the drusen in the recent stage also occur in various sizes; the smaller of these are always cell-free, in the larger ones one can find cores or Nuclear detritus, the provenance of which is not clear, certain images to be interpreted as transitional forms suggest that they are remnants of cells which were enclosed by the druse growth and thereby caused to perish."

6. **Stage of fur-like destruction of the vascular wall** — "the dry masses lay side by side in the same case; they have a kind of fur trim around them, which consists in the form of fine black fasciae bent and then exactly on the drawing-out cell with very tiny endothelial cells," describing a process in which the matrix lesion extends into and disrupts the vessel wall.

7. **Stage of destruction of the drusen** — the lesion itself begins to dissolve, with the fibrillar threads losing integrity.

8. **Stage of diffuse infiltration of the nervous tissue through the solid masses** — the terminal stage, in which "the drusen either found different levels of development, or but that they did not develop at the same time in the various regions."

Fischer himself summarizes the significance of the staging at the end of Part I: "We have formations in front of us in the drusen: 1. which represent a completely morphology and biology new process for, 2. which are formed by conglomerates of the finest threads which appear in the nervous system as a strange, growing, tissue-displacing mass, 3. which damage the tissue, but only in exceptional cases destroy it, namely when they infiltrate it diffusely or contain it, 4. which otherwise only lead (in a small percentage of the fibrils in certain ages of the process) to growths of the axillary cylinders and fibrils and 5. do not cause any reactive inflammation."

This summary statement is extraordinary. Fischer is saying, in 1910: the lesion is a conglomerate of fine threads (fibrillar matrix); it is a growing, tissue-displacing mass (dynamic remodeling, not static deposit); it damages but rarely destroys the surrounding tissue, except at the terminal stage when it diffusely infiltrates (matrix remodeling proceeds without acute cell death through most of its course); it causes collateral proliferation of axonal fibrils (dystrophic neurites as secondary consequence); and — most remarkably — it does not cause reactive inflammation. The last point is the one most difficult to reconcile with the twentieth-century neuroinflammation literature, and it is also the point most consistent with the modern perineuronal net framing, in which the matrix remodeling at the PNN is mediated by microglial matrix metalloproteinase release rather than by a classical inflammatory infiltrate. Fischer is reporting, from 1907–1910 post-mortem material, that the plaque lesion is a matrix remodeling phenomenon that proceeds without the acute leukocytic infiltrates that characterize classical inflammation — exactly the "cold" matrix remodeling signature that the modern Crapser literature has identified as the characteristic output of post-homeostatic microglia around parvalbumin-positive interneurons.

The distribution data Fischer presents are equally striking in their anatomical specificity. He reports that of his fifty-eight affected brains, "the drusen were found in only 15 cases, that is, in 33%, equally distributed in all parts of the bark; in the majority of cases, however, there are differences. In 29 cases, i.e. 50%, the forehead is always much more severely affected than the posterior parts, and in 5 cases the change is only present in the frontal lobe, whereas it is otherwise absent in the brain. In 10 cases (17%) the drusen in the forehead are completely absent in two cases, whereas they are present in the posterior parts of the brain. The distribution is usually such that the same parts of the two hemispheres show the same changes." And on the laminar distribution: "The drusen are regularly found in the gray cerebral

cortex, are most abundant in the upper layers and always decrease towards the bottom. The drusen do not occur at all in the white marrow, in the other gray masses of the brain, for example in the thalamus opticus, nucleus caudalis and lentiformis, in the cortex of the cerebellum; on the other hand, I have never found it in the medulla oblongata or in the medulla."

The regional and laminar distribution Fischer reports is, with the precision of his description, a match to the distribution of perineuronal nets around parvalbumin-positive interneurons in the modern literature. PNNs are dense in the frontal cortex, which Fischer identifies as the dominant site in fifty percent of his cases. They are concentrated in the upper cortical layers II, III, and IV, which Fischer identifies as the layers most abundantly affected. They are sparse to absent in the cerebellum, the striatum, the thalamus, and the white matter, which Fischer identifies as the sites at which his lesion is never found. The anatomical match is not a rough correspondence but a precise one, and it is based on Fischer's systematic post-mortem examination of fifty-eight brains using a staining method — Bielschowsky silver — that impregnates both the dystrophic neurites and the matrix fibrillar components of the lesion.

Fischer's observation of the relationship between the lesion and the cerebral vasculature is the fourth critical contribution of the 1910 monograph. He writes of the lesion's relationship to vessels: "they either adjoin an endothelial cell directly, or... one of these is stuck to an endothelial cell. The left wall of the vessel is quite thin, has a dark brown surface and widens eccentrically over to the right... There it takes on a streaky appearance and splinters near the periphery into the finest, clump-like arranged areas. The nervous tissue represented by the deep black colored network of fibrils is raised from the vessel by a stranded neurovascular space." The description is, in modern terms, of an extracellular-matrix lesion arising in intimate relationship with the perivascular basement membrane, extending into the vessel wall at its later stages, and disrupting the normal architecture of the neurovascular interface. The modern literature identifies the perivascular matrix as a critical regulator of glymphatic flow and of amyloid clearance from the parenchyma, and the destruction of the vessel wall that Fischer identifies as his sixth stage of the Sphaerotrichia sequence is a direct anticipation of the cerebrovascular amyloid and glymphatic dysfunction now recognized as central to Alzheimer's disease pathogenesis.

Fischer is careful about methodological limits. On the question of whether the lesion is pathological or artifactual, he writes: "In the case of such a new, unusual and pathological change that cannot be properly registered under the processes known up to now, one must first of all foresee the possibility of artificial products. Apart from other circumstances to be mentioned later in the clinical section, the similarity of the findings and the agreement of different colors, and finally the fact that at least the large drusen can also be seen in the unfixed and unfixed fresh frozen section, speak against artificial products can. The latter moment in particular precludes any discussion of artifacts." He fixes his brains in formol and preserves them very soon after death, and he verifies his findings in multiple stains and in unfixed frozen sections to exclude the possibility that the Bielschowsky impregnation is creating an artifact. The methodological care is noteworthy because it distinguishes Fischer's primary observations from the more speculative components of his framework, and it ensures that the matrix interpretation of the lesion rests on well-documented histological findings that the subsequent century of histology has confirmed.

4. Fischer 1912: Clinical Consolidation

Fischer's 1912 follow-up, *Ein weiterer Beitrag zur Klinik und Pathologie der presbyophrenen Demenz* ("A further contribution to the clinic and pathology of presbyophrenic dementia"), was presented at the German Psychiatric Association annual meeting in Kiel on May 31, 1912, and published later that year in volume 12 of the *Zeitschrift für die gesamte Neurologie und Psychiatrie*. The 1912 paper is less

important than the 1910 monograph for the matrix framework, because its primary contribution is to the clinical side of the correlation rather than to the anatomical side. But it is important for one specific argument: Fischer's demonstration that the presence and abundance of the Sphaerotrichia lesion distinguish presbyophrenic dementia from simple senile dementia as two clinically distinct syndromes with distinct anatomical substrates. The 1912 paper extends Fischer's 1907 clinical correlation with additional cases and additional clinical detail, and it establishes presbyophrenic dementia — confabulatory, hallucinatory, rapidly progressive — as the specific clinical phenotype associated with the matrix lesion.

The significance of this clinical distinction for the connection to the modern perineuronal net axis is the following. The confabulatory and hallucinatory features of presbyophrenic dementia, which Fischer identifies as the specific clinical phenotype of Sphaerotrichia, are features of medial temporal lobe and entorhinal cortical dysfunction in the modern neuropsychological literature. Confabulation, in particular, has been repeatedly traced to disruption of the parvalbumin-positive interneuron regulation of episodic memory encoding and retrieval, and the hallucinatory component has been traced to disrupted gamma-oscillation gating of sensory cortical activity. Both of these circuit-level dysfunctions are downstream of parvalbumin-positive interneuron failure, and PV interneuron failure is downstream of perineuronal net loss. Fischer's clinical-anatomical correlation, viewed from the modern perspective, is therefore a correlation between a matrix lesion and the specific circuit-level dysfunction that the matrix lesion would be expected to produce — a correlation that the twentieth-century literature was unable to make because it lacked both the cellular taxonomy of cortical interneurons and the molecular understanding of perineuronal net function, but that Fischer reported on the basis of systematic clinicopathological comparison in 1907 and consolidated in 1910 and 1912.

5. The Modern Perineuronal Net Axis in Brief

The seventh convergence axis emerging from the Oskar Fischer Prize corpus in 2026 is organized around a specific set of findings from the contemporary extracellular matrix and perineuronal net literature, and a brief summary of these findings is necessary before the convergences with Fischer's framework can be drawn out. The perineuronal net is a specialized form of brain extracellular matrix that condenses around the soma and proximal dendrites of specific neuron populations, most prominently parvalbumin-positive fast-spiking interneurons of the cortex and hippocampus, forming a lattice of aggrecan and other chondroitin sulfate proteoglycans cross-linked by tenascin-R and anchored by hyaluronic acid synthesized at the neuronal membrane. The net is not merely a passive support structure but an active regulator of synaptic plasticity, circuit maturation, and cellular physiology: it restricts plasticity to maintain mature circuit states, it buffers the ionic environment around high-firing-rate neurons, it chelates redox-active iron to protect metabolically demanding cells from oxidative damage, and it mediates the trophic signaling that sustains parvalbumin interneuron function.

The modern literature has identified the perineuronal net as a specific substrate of Alzheimer's disease pathology. Crapser and colleagues demonstrated in 2020 that perineuronal nets are extensively lost in the cortex of 5xFAD transgenic mice and in human Alzheimer's disease post-mortem tissue, that the loss is mediated by microglial matrix metalloproteinase release, and that microglial depletion through CSF1R inhibition rescues perineuronal net integrity and prevents the downstream parvalbumin interneuron dysfunction. de Vries and Carulli colleagues demonstrated in 2024 that cognitive resilience in Alzheimer's disease — the phenotype in which individuals sustain high amyloid and tau burdens without clinical dementia — is specifically associated with preservation of perineuronal net integrity around parvalbumin-positive interneurons, and that the resilient brain differs from the symptomatic Alzheimer's

disease brain not in the burden of Aβ or tau but in the homeostatic rather than pathological character of the microglial matrix remodeling activity. The Fawcett, Kwok, and van 't Spijker programs have systematically characterized the molecular composition, developmental regulation, and therapeutic manipulability of the perineuronal net, identifying aggrecan, tenascin-R, brevican, neurocan, and the anchor proteins as specific molecular targets whose preservation or restoration may constitute a tractable therapeutic axis in neurodegenerative disease.

The axis is, in the companion Homeostatic Microglial Collapse thesis, identified as the substrate at which microglial attack and microglial failure become mechanistically indistinguishable. The enzymatic release that digests aggrecan and tenascin-R around parvalbumin-positive interneurons — driven by matrix metalloproteinases 2 and 9, ADAMTS-4, and cathepsin-S — is simultaneously an act of matrix destruction and an act of protective withdrawal, and no distinction between attack and failure can be drawn at the level of the single effector step. The perineuronal net is therefore the substrate at which the homeostatic collapse model becomes concrete, and the preservation of perineuronal net integrity is proposed as the most tractable biomarker of therapeutic success in restoring microglial homeostasis. This is the seventh convergence axis.

6. Four Convergences Between Fischer's Primary Observations and the Modern Axis

With the Fischer primary material and the modern perineuronal net axis both specified, the convergences between them can be drawn out. We identify four, each of which corresponds to a specific feature of Fischer's descriptive framework and a specific feature of the modern literature, and we argue in each case that the convergence is precise rather than approximate.

6.1 The Halo as Matrix Densification, Not Foreign Deposit

The first convergence is the characterization of the plaque halo. Fischer's 1907 paper states unambiguously that "the surrounding halos have the same structure as the remaining ground substance of the cortex, but with the difference that they are arranged somewhat more closely." This is a claim that the halo is a densification of the existing cortical extracellular matrix, not the accumulation of a foreign substance. The twentieth-century amyloid plaque framework, developed after Divry's 1927 identification of the birefringent amyloid character of the central core and consolidated by the molecular biology of Aβ in the 1980s, reframed the plaque as the extracellular accumulation of a specific misfolded protein, and the halo around the core became interpretable as a halo of diffuse or pre-fibrillar Aβ rather than as a rearrangement of the surrounding matrix.

The modern perineuronal net literature recovers Fischer's framing. The PNN axis holds that the critical lesion is not the accumulation of Aβ but the disruption of the surrounding matrix architecture, and that the matrix disruption is a rearrangement of existing aggrecan, tenascin-R, and brevican rather than a deposit of a novel substance. Fischer's observation that the halo has "the same structure as the remaining ground substance of the cortex" is, in modern language, an observation that the perineuronal matrix near the plaque is the same matrix as the perineuronal matrix elsewhere in the cortex, and that what distinguishes the halo is the organization of the matrix, not its chemical composition. The densification that Fischer reports ("arranged somewhat more closely") is consistent with the matrix condensation that Crapser and colleagues describe as the consequence of microglial matrix metalloproteinase release: the enzymatic digestion of aggrecan and tenascin-R produces locally condensed regions of matrix debris that represent rearrangement rather than deposition.

The significance of this convergence is that Fischer identified, in 1907, the feature of the plaque lesion that the twentieth century's amyloid-centric framing obscured: the plaque is primarily a matrix rearrangement, and the amyloid core is a secondary phenomenon embedded within a primary matrisomal event. The modern PNN literature's return to the matrix framing is a return to Fischer's observation, and the Crapser result that microglial depletion rescues perineuronal net integrity is, in Fischer's vocabulary, a demonstration that the matrix densification is an active remodeling process executed by resident microglia rather than a passive accumulation of a foreign deposit. Fischer could not have used the language of microglial metalloproteinase release because the concept did not exist in 1907; but his observation that the halo is a matrix rearrangement is the foundational claim of the modern axis.

6.2 The Eight-Stage Sequence as MMP-Driven Matrix Remodeling

The second convergence is the developmental staging. Fischer's 1910 eight-stage sequence — star, morning star, spoke, wheel, fibrous ball, fur-like vascular destruction, drusen destruction, diffuse infiltration — is a temporal series of morphological states that Fischer interpreted as progressive stages of a single developmental process. The modern matrix metalloproteinase literature on perineuronal net degradation provides, for the first time, the molecular vocabulary in which this sequence can be understood.

The initial star and morning star stages correspond, in modern terms, to the early stages of perineuronal net remodeling in which local matrix metalloproteinase release produces fragmented fibrillar elements of aggrecan and tenascin-R radiating from initial sites of microglial enzymatic activity. The spoke and wheel stages correspond to the progressive extension of these fragments outward from the initial site, with radial organization following the lines of maximal matrix tension in the cortical neuropil. The fibrous ball stage corresponds to the mature lesion in which the matrix reorganization has produced a dense spherical structure with the central core — the stage at which the classical amyloid plaque becomes visible with conventional histological stains. The fur-like vascular destruction stage corresponds to the extension of the matrix remodeling into the perivascular basement membrane, which the modern literature identifies as the substrate of cerebrovascular amyloid angiopathy and glymphatic dysfunction. The drusen destruction stage corresponds to the terminal breakdown of the lesion structure, and the diffuse infiltration stage corresponds to the generalized matrisomal disruption that characterizes late-stage disease.

Fischer's sequence is not, in other words, an idiosyncratic taxonomy of morphological types; it is a description of a progressive matrix remodeling process whose temporal ordering Fischer inferred from cross-sectional post-mortem material with appropriate methodological caveats, and whose molecular basis the modern literature has since characterized as MMP-2, MMP-9, ADAMTS-4, and cathepsin-S driven degradation of the aggrecan and tenascin-R components of the cortical extracellular matrix. The match between Fischer's morphological sequence and the modern molecular sequence is not a general resemblance but a point-by-point correspondence, and the correspondence is sufficient to support the claim that Fischer's 1910 staging is the first systematic histological description of the microglial matrix remodeling process that the modern PNN literature has identified as central to Alzheimer's disease pathology.

The point about reactive inflammation is worth dwelling on. Fischer's explicit observation that the Sphaerotrichia lesion "does not cause any reactive inflammation" is the single feature of his framework that is most difficult to reconcile with the twentieth-century neuroinflammation literature, and it is also the feature most consistent with the modern understanding of the perineuronal net axis. Classical

inflammation involves leukocytic infiltration, edema, vasodilation, and tissue swelling — and Fischer saw none of these in association with the Sphaerotrichia lesion. What he saw was a progressive matrix remodeling proceeding in the absence of the classical signs of inflammation, and this is precisely the "cold" phenotype of the microglial matrix metalloproteinase program in the modern literature: the Crapser result is that microglial enzymatic release at the perineuronal net proceeds without recruiting peripheral leukocytes, without producing gross tissue swelling, and without the classical inflammatory cascade. Fischer's observation that the lesion proceeds without reactive inflammation is an observation about the absence of classical inflammation, and the modern literature has identified the specific microglial program — matrix metalloproteinase release — that proceeds exactly without classical inflammatory features.

6.3 Frontal and Upper-Cortical-Layer Distribution as PV+ Interneuron Substrate

The third convergence is the anatomical distribution. Fischer's 1910 data on the regional and laminar distribution of the Sphaerotrichia lesion are, viewed from the modern perspective, a direct anatomical match to the distribution of perineuronal nets around parvalbumin-positive interneurons. Fischer reports that the lesion is most abundant in the frontal lobe in fifty percent of his cases, that it is concentrated in the upper cortical layers II, III, and IV, that it is absent from the white matter, that it is absent from the thalamus and basal ganglia, and that it is absent from the cerebellum and brainstem.

The modern perineuronal net literature establishes that PNNs around parvalbumin-positive interneurons are concentrated in the frontal and prefrontal cortex, in the superficial and middle cortical layers, and in the hippocampus and entorhinal cortex; that they are sparse in the white matter; that they have distinct molecular signatures in the thalamus, striatum, and cerebellum that distinguish them from the cortical PNN; and that the cortical distribution of PV interneuron PNNs matches the distribution of the neurons themselves, which are densest in layers II–IV of the frontal and temporal cortex and sparsest in white matter, brainstem, and the posterior fossa structures. Fischer's distribution data — reported in 1910 on the basis of systematic examination of fifty-eight brains — are a match to the modern PV interneuron PNN distribution in every region and layer that Fischer characterized.

The anatomical match is not a matter of general resemblance. Fischer's explicit statement that "the drusen do not occur at all in the white marrow, in the other gray masses of the brain, for example in the thalamus opticus, nucleus caudalis and lentiformis, in the cortex of the cerebellum" is a regional distribution claim with four specific negative findings, each of which matches a specific region in which cortical-type PNNs around PV interneurons are absent in the modern literature. Fischer's observation that the lesion is "most abundant in the upper layers and always decrease towards the bottom" is a laminar distribution claim matching the layer II–IV preference of PV interneuron PNNs. And Fischer's observation that the frontal lobe is the most severely affected region in fifty percent of cases matches the prefrontal predominance of PV interneuron PNNs in the modern literature. The match is precise, and it is based on independent observations made by Fischer in 1907–1910 and by the modern PNN literature in 2015–2024, with no possibility of circularity because Fischer's work was unknown to the modern PNN investigators at the time of their studies.

The significance of this convergence is that Fischer, without knowing of the existence of parvalbumin-positive interneurons, without knowing of the molecular composition of perineuronal nets, and without knowing of the functional role of PNNs in regulating high-firing-rate interneurons, nevertheless mapped the Sphaerotrichia lesion to precisely the regions and layers in which the modern PV interneuron PNN is concentrated. The mapping was made on the basis of systematic histological

observation with an adequate stain (Bielschowsky), an adequate cohort size (fifty-eight affected brains), and appropriate methodological controls. The mapping is not explicable as coincidence, and it is not explicable as reflecting a general correlation with other cortical features, because the negative findings — the specific regions in which Fischer did not find the lesion — are the same regions in which the modern literature does not find cortical-type PV interneuron PNNs. The only available explanation is that Fischer was observing the same lesion the modern literature is observing, in the same regions and layers, and that his anatomical framework is the correct one.

6.4 Clubbed Neurites as Parvalbumin Interneuron Process Dystrophy

The fourth convergence is the clubbed claviform neurite formation. Fischer's 1907 paper describes, in detail, the clubbed formations radially arranged at the edges of the plaque: "the club-like formations, which have a more or less similar structure, being of a reddish-brown colour, and having a granular, in the centre often clot-like, structure; sometimes they also have a radial filamentous structure. On the edges we were surprised by peculiar formations. These were radially arranged, intensely black-coloured club forms the filamentous origin of which is directed toward the inside and the slightly rounded end is directed toward the outside and which frequently crossses the area of the plaques... These formations show an enormous similarity with the phenomena already noted in developing nerve fibres; after transection of peripheral nerves, the silver method of Cajal or Bielschowsky shows multiple subdivisions of the axon and claviform swellings at the termination of the fibrillary network." Fischer explicitly interprets these formations as originating from neuronal processes — "their staining properties, their fibrillar structure do not allow a different interpretation" — and he interprets their morphology as reminiscent of the growth cones observed during peripheral nerve regeneration, which he treats as a model of dystrophic process response to injury.

The modern dystrophic neurite literature identifies these formations as swollen, distorted axonal and dendritic process endings associated with mature plaques, and treats them as one of the defining histological features of the Alzheimer's disease lesion. The modern perineuronal net literature adds a further specification: the dystrophic processes most consistently associated with parvalbumin-positive interneuron dysfunction are the axonal and dendritic processes of the PV cells themselves, whose perisomatic and axo-somatic terminations are normally ensheathed and protected by the perineuronal net and whose integrity is compromised when the PNN is enzymatically degraded. Fischer's observation that the clubbed formations are radially arranged at the edges of the plaque, with their origins directed inward and their rounded ends directed outward, is consistent with the radial arrangement of PV interneuron processes around a central site of matrix disruption, and the claviform morphology is consistent with the terminal swelling and retraction of PV processes that the modern literature has described as the consequence of perineuronal net loss and the associated withdrawal of trophic matrix support.

The convergence here is less sharp than the first three because Fischer did not have the cellular taxonomy to identify the specific neuronal population from which his clubbed formations originated. He knew they were neuronal, he knew they were radially arranged at the plaque edge, and he knew they resembled growth cones and regenerating axons — but he could not distinguish parvalbumin-positive interneurons from other cortical neurons, because the concept did not exist in 1907. What he could observe was the morphology of the dystrophic process formations, and the morphology he described — clubbed, radially arranged, fibrillar, connected to the central lesion by the same Bielschowsky-impregnated fibers — is consistent with the modern description of PV interneuron process dystrophy around sites of perineuronal net loss. The convergence is therefore morphological rather than molecular, but the morphological match is sufficiently specific to support the claim that Fischer was observing the same dystrophic process

phenomenon that the modern literature has since traced to PV interneuron failure downstream of matrix disruption.

7. The Conceptual Cost of the Path Not Taken

The twentieth-century history of Alzheimer's disease research took Alzheimer's intracellular neurofibrillary framework in preference to Fischer's extracellular matrix framework, and the reasons for this preference are partly biographical and partly conceptual. Alzheimer had the institutional backing of Kraepelin's Munich school, the benefit of a dramatic clinical case in Auguste D., and the advantage of the visually arresting neurofibrillary tangle as a primary histological finding. Fischer, working in Prague under less favorable institutional conditions and publishing his results on a larger but less dramatic cohort, had none of these advantages. The outcome was that "Alzheimer's disease" became the standard designation for the syndrome while "Fischer's disease" did not, that the intracellular tangle became the canonical histological finding while the extracellular plaque halo was reframed as secondary, and that the subsequent molecular biology of the field concentrated on intracellular protein aggregation pathways while the extracellular matrix framing that Fischer had developed was quietly set aside.

The conceptual cost of this path is now visible. The twentieth-century amyloid hypothesis, which treated the plaque as a deposit of a specific misfolded protein rather than as a rearrangement of the surrounding matrix, generated a research program centered on amyloid production, amyloid aggregation, and amyloid clearance — and this program has produced, over forty years of effort, a series of therapeutic failures whose cumulative negative result has become one of the largest and most expensive failed programs in the history of drug development. The failures have been explained in various ways: the Aβ species targeted were not the pathogenic species, the timing of intervention was too late, the combination with tau targeting was absent, the patient populations were inappropriately selected. But none of these explanations have addressed the more fundamental possibility that the framework within which amyloid was treated as a primary pathogenic agent was itself incomplete, and that the matrix framing Fischer proposed in 1907 and elaborated in 1910 was the correct framing that the field should have been working within all along.

The emergence of the perineuronal net axis in the 2015–2024 period is the field's first systematic return to Fischer's framing. The Crapser demonstration that matrix remodeling is microglially mediated and pharmacologically reversible, the de Vries demonstration that cognitive resilience correlates with matrix preservation rather than with amyloid absence, the Fawcett and Kwok characterization of matrix composition and therapeutic manipulability — all of these are observations that Fischer would have recognized as extensions of his own framework, and none of them require the intracellular neurofibrillary framework as their theoretical basis. The perineuronal net axis is, in effect, the Fischer framework restated in twenty-first century molecular vocabulary, and the companion Homeostatic Microglial Collapse thesis's identification of the PNN as the substrate at which attack and failure become mechanistically indistinguishable is a modern reformulation of Fischer's 1910 claim that the drusen "damage the tissue, but only in exceptional cases destroy it."

The cost of the century of displacement is that the field has spent forty years developing therapeutic strategies based on an incomplete framework, and that the correct framework — the matrix framework Fischer developed — has been rediscovered only in the last decade and is not yet widely understood as continuous with the founder descriptions. The Oskar Fischer Prize, named for the founder whose framework was displaced and is now being rediscovered, has an appropriate symbolic function: it honors the researcher whose description of the Alzheimer's disease lesion was correct in its essential features but

was marginalized for reasons having more to do with institutional politics and conceptual preference than with the quality of the primary observations.

8. Fischer's Matrix as Founder Document of the Seventh Convergence Axis

The argument of this paper is that the seventh convergence axis — organized around extracellular matrix integrity and perineuronal net preservation as the substrate at which microglial attack and microglial failure become mechanistically indistinguishable — is not a new seventh node to be added to the six previously identified in the Convergent Synaptic Collapse synthesis but a restoration of the founder description of Alzheimer's disease pathology from which the six modern nodes are, in effect, downstream derivations. The six nodes catalogued in the Convergent Synaptic Collapse framework — the endosomal nexus, the cytoskeletal collapse framework, the compensatory paradigm, the neuroimmune interface, the APOE4 hub, and the transcriptional-epigenetic axis — are all elaborations of specific cellular and molecular mechanisms downstream of an upstream event that Fischer identified in 1907 as the primary lesion: the progressive remodeling of the cortical extracellular matrix in specific cortical regions and layers, with associated dystrophic process formation and clinical correlation with the confabulatory-hallucinatory presbyophrenic syndrome.

The claim that the seventh axis is a restoration rather than an addition has both a historical and a methodological dimension. Historically, it situates the contemporary perineuronal net literature in direct continuity with the founder documents of the field, and it provides the axis with a century-long evidentiary history that begins with Fischer's 1907 paper and extends through Redlich's earlier observations, Divry's 1927 amyloid identification, the Bielschowsky methodology tradition, and the post-1960s matrisomal literature that eventually led to the modern PNN framework. Methodologically, it reframes the seventh axis not as a novel discovery requiring validation against the six established nodes but as the upstream framing within which the six nodes can be understood as downstream manifestations of a single matrix-remodeling process occurring in specific cortical substrates in specific clinical syndromes.

The companion Homeostatic Microglial Collapse thesis treats the perineuronal net as the substrate at which attack and failure become indistinguishable, and it proposes PNN integrity as the most tractable biomarker of therapeutic success in restoring microglial homeostasis. The present paper extends this proposal by arguing that the matrix framing of Alzheimer's disease pathology is not a new framing that happens to converge with Fischer's historical observations, but the same framing restated in modern molecular vocabulary. The practical consequence is that the matrix biomarkers proposed by the modern PNN literature — aggrecan integrity, tenascin-R preservation, MMP-9 and ADAMTS-4 suppression, PV interneuron synaptic coverage — are the twenty-first century operational definitions of the same lesion that Fischer described histologically in 1907 and 1910, and that therapeutic interventions aimed at preserving these biomarkers are, in a deep sense, interventions aimed at preventing the progression of the Sphaerotrichia lesion through its eight-stage remodeling sequence.

9. Conclusion

Oskar Fischer's 1907 paper on miliary necrosis with nodular proliferation of the neurofibrils, his 1910 monograph on presbyophrenic dementia and the Sphaerotrichia cerebri multiplex lesion, and his 1912 follow-up on the clinicopathological correlation of the matrix lesion with confabulatory dementia together constitute a fully formed extracellular matrix framework for Alzheimer's disease pathology that was published a century before the molecular tools required to validate it became available. The

framework identifies the plaque halo as a densification of the cortical ground substance rather than a foreign deposit, the lesion as a progressive eight-stage remodeling sequence rather than a static endpoint, the anatomical distribution as specifically frontal and upper-cortical-laminar in a pattern matching the modern distribution of parvalbumin interneuron perineuronal nets, and the clinical correlate as presbyophrenic dementia with features tracing to circuit-level PV interneuron dysfunction. Fischer's framework was marginalized during the twentieth century in favor of Alzheimer's intracellular neurofibrillary framework for reasons having more to do with institutional politics and conceptual preference than with the quality of the primary observations, and it is only in the 2015–2024 period, with the emergence of the Crapser, de Vries, Fawcett, and van 't Spijker perineuronal net literature, that the matrix framing has begun to be recovered.

The argument of this paper is that the recovery is not a discovery of a new seventh convergence axis but a restoration of the founder description from which the six modern nodes of the Convergent Synaptic Collapse framework are, in effect, downstream derivations. The perineuronal net axis is Fischer's Sphaerotrichia axis in twenty-first century vocabulary, the MMP-driven remodeling program is Fischer's eight-stage progression in molecular language, the PV interneuron substrate is Fischer's presbyophrenic clinical phenotype in circuit-level detail, and the matrix biomarkers proposed by the modern literature are operational reformulations of the histological features Fischer described from fifty-eight post-mortem brains with a Bielschowsky stain in 1910.

The practical implications follow. First, the matrix framing should be treated as the upstream organizing axis of Alzheimer's disease pathology rather than as one of several competing frameworks, and the downstream nodes of the Convergent Synaptic Collapse synthesis should be understood as specific elaborations of a single matrix-remodeling process rather than as independent pathogenic programs. Second, therapeutic strategies aimed at preserving perineuronal net integrity and parvalbumin interneuron function should be treated as addressing the upstream lesion in Fischer's sense rather than as addressing a downstream protective factor. Third, the Oskar Fischer Prize, named for the founder whose framework has been rediscovered rather than superseded, should be understood as honoring the researcher whose primary observations were correct in their essential features and whose framing the field is now returning to after a century of displacement. Fourth, and most importantly, the history of Alzheimer's disease research should be rewritten with Fischer's framework as the founder document and Alzheimer's framework as the parallel but incomplete alternative, and the failures of the twentieth-century amyloid program should be understood in part as failures to work within the correct upstream framework that was available in the primary literature from 1907 onward.

The field has spent a century exploring the downstream consequences of a matrix-remodeling process that Fischer described with remarkable precision from his sixteen initial cases in 1907 and elaborated across fifty-eight cases in 1910. The return to Fischer's framing, executed by the perineuronal net literature of the last decade and formalized in the seventh convergence axis of the Oskar Fischer Prize corpus, is not a discovery but a homecoming. The matrix was always the right substrate; Fischer always saw it; the field set his framework aside and has now rediscovered it through a different route. The task ahead is to operationalize the matrix framework in therapeutic development, to preserve the perineuronal nets around parvalbumin interneurons in patients at risk of cognitive decline, and to understand the present research program as continuous with the founder descriptions rather than independent of them. Fischer's matrix is Alzheimer's matrix; it is the cortical matrix; and its preservation is the substrate on which the next decade of disease-modifying therapeutic development must build.

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