The Staged Deposit

Oskar Fischer's morphology of the plaque, 1907–1912, read against the modern evidence — how the lesion was staged before it was counted, and why its morphology and not its number is the variable that tracks injury

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In 1910 Oskar Fischer reported that club-shaped abnormal neurites were present in about half of the plaques he examined, that they occurred almost entirely at the two latest stages of his developmental series, and that the two earliest stages carried none at all. Neuritic injury, on his own data, was not a property of the presence of a plaque but of the plaque's stage. The century that followed replaced the stage with a tally.

Prepared for Dr. James Truchard and Benjamin Gustafsson
Drafted by Claude-Opus-5
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Abstract

Between 1907 and 1912 Oskar Fischer published three studies of the senile plaque that together constitute the largest and most systematic morphological description of the lesion made in the first half of the twentieth century. In the 1910 monograph he distinguished eight types of plaque, of which the first five he held to form a developmental continuum from a small radial star to a large fibrous ball with a core, and the last three to describe the lesion's fates: infiltration of the vessel wall, dissolution of the deposit, and diffuse infiltration of the surrounding tissue. Alongside the staging he reported an observation that has almost never been cited since. Club-shaped abnormal neurites were present in roughly half of the plaques he examined; they were found almost entirely at his stages IV and V, occasionally at III, and never at I or II. Neuritic injury, on Fischer's own data, was not a property of the presence of a plaque. It was a property of the plaque's stage.

This paper argues that Fischer's staging is the century-old form of a measurement the field has only recently begun to make again, and that the intervening century of counting plaques was, in a specific and demonstrable sense, the substitution of a weaker variable for a stronger one. Three independent modern literatures have converged on the proposition that at fixed plaque number the morphology of the deposit determines the injury around it. High-resolution imaging shows that microglia form a physical mantle around the deposit, compacting it and holding protofibrillar amyloid off the surrounding neuropil, and that where the mantle is thin the deposit is filamentous and the neurites around it are severely dystrophic; the human demonstration comes from *TREM2* R47H carriers, in whom plaque burden is unchanged and peri-plaque axonal dystrophy and phospho-tau are markedly increased. Quantitative neuropathology across forty subjects with symptom durations from four to twenty years finds plaque burden essentially stationary while dystrophic neurites and CD68-positive microglia *per plaque* rise significantly with duration. And a 2022 reclassification of the dense-core plaque as a granuloma — a compact organised collection of mononuclear phagocytes formed around a stimulus that cannot be resolved — restores, without citing him, precisely the comparison Fischer chose in 1907, when he named the lesion *drüsige Nekrose* and likened it to the radially organised granule of actinomycosis.

We set out Fischer's record with its numbers corrected against the primary literature, map each of his eight types onto the modern description of that morphology, and state where the mapping holds and where it fails. Two of his stages are read here in a direction opposite to his own. Stage VI, the infiltration of the vessel wall, he took to be the deposit invading the vessel; the modern account of cerebral amyloid angiopathy runs the other way, along the perivascular drainage route, and it was from meningeal vessels rather than from plaque cores that the amyloid protein was first purified. Stage VII, the dissolution of the deposit, has now been produced deliberately in living patients by active and passive immunisation, and the long-term follow-up of the first such trial found that virtually complete plaque removal did not prevent progression to severe dementia — which makes Fischer's terminal stage the most instructive of the eight, because it is

the one modern medicine has achieved and the achievement did not deliver what counting predicted it would.

We also examine, and decline, a reading of Fischer that has attracted recent interest: that he was the founder of an extracellular-matrix theory of the disease which the amyloid era displaced. His own conclusion, stated in 1912, was that the plaque is a proteinaceous metabolic product of the brain — a position closer to the amyloid framing than to the matrix one, and one the isolation of the amyloid-β peptide in 1984 and 1985 substantially vindicated. The matrix does bear on his observations, but not in the way that reading requires: the cortical areas richest in extracellular-matrix proteoglycans are the areas *least* affected by the cytoskeletal pathology of the disease, and the relationship between proteoglycan-rich territory and amyloid deposition shows no precise correspondence. Fischer's regional map is therefore not the perineuronal-net map. For tau it is closer to its negative image, which is what a protective reading of the net predicts and a matrix-lesion reading does not.

The paper closes with an operational restatement of Fischer's staging in measurable terms — compaction, mantle coverage, halo extent, neuritic dystrophy — with the four falsifying observations that would break it, a statement of what the scheme does not cover, and a graded summary of the strength of each claim. The argument is not that Fischer anticipated the molecular biology. It is narrower and, we think, more useful: he was measuring the right variable, he was measuring it well, and the field replaced it with a tally.

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Part One — The Record

I. The Count and the Stage

The senile plaque is the most counted object in the history of neuropathology, and the count has never worked very well.

The difficulty is old and it is not in dispute. Katzman's 1988 series described elderly subjects who functioned in the top quintile of their cohort until death and whose brains nonetheless carried roughly four-fifths as many neocortical plaques as the demented, meeting the pathological criteria of the disease [1]. Community-based autopsy series have replicated the observation many times over: a substantial fraction of cognitively unimpaired elders meet neuropathological criteria for Alzheimer's disease at death [2]. Working from the other direction, Terry and colleagues established in 1991 that the strongest neuropathological correlate of antemortem cognitive severity is not plaque count or tangle count but synapse loss [3]. Perez-Nievas and colleagues, comparing resilient with demented brains matched for tangle burden, found the resilient brains distinguished not by fewer tangles but by markedly less fibrillar and plaque-associated oligomeric amyloid deposited *in situ*, no selective accumulation of soluble tau into the synaptic compartment, and less glial activation [4].

The field has drawn two conclusions from this. The first is that the plaque is epiphenomenal — a tombstone rather than a cause. The second is that the wrong species was counted, and that the pathogenic agent is the soluble oligomer, which the plaque merely sequesters. Both are serious positions and both have generated productive work.

There is a third possibility, and it is rarely stated because it concerns the arithmetic rather than the biology. A count is a summary statistic, and it is the correct summary statistic only for a population of objects that are interchangeable. If the objects differ from one another in a way that determines their local effect, then counting them discards exactly the information that decides the outcome. A brain with two hundred plaques of which forty are injuring the surrounding neuropil is not the same brain as one with two hundred plaques of which one hundred and sixty are, and no count can tell them apart. On this reading the failure of plaque burden to predict dementia is not evidence that plaques do not matter. It is evidence that *plaques* is the wrong unit — that the population is heterogeneous, and that the heterogeneity is the signal.

This is not a new idea. It is the assumption on which the lesion was originally described, and it was abandoned rather than refuted.

Oskar Fischer, working in Prague between 1907 and 1912, did not count plaques. He staged them. Across three publications — a sixteen-case report in 1907, a monograph on two hundred and seventy-five brains in 1910, and a clinical consolidation in 1912 — he distinguished eight morphological types of the lesion, argued that the first five formed a developmental continuum, and reported that the abnormal club-shaped neurites which are the plaque's visible injury to the surrounding tissue occurred in roughly half of the plaques he examined, almost entirely at the two latest stages of that continuum, and never at the two earliest [5]. That last observation is a statement that neuritic injury is conditional on plaque morphology, made on a per-lesion basis, with each brain serving as its own control, in 1910.

The twentieth century did not build on it. Divry's 1927 demonstration that the plaque core is birefringent after Congo red staining redirected attention to the chemical identity of the core [6]; the isolation of the amyloid-β peptide in the mid-1980s completed that redirection [7,8]; and the diagnostic instruments the field settled on — the CERAD neuritic-plaque score, the Thal phase — are, whatever their other virtues, density and distribution measures rather than morphological ones. The stage was replaced by the tally.

The purpose of this paper is to take Fischer's staging seriously as a measurement, set it against what is now known about each of the morphologies he described, and ask what the substitution cost. The answer we arrive at is that three modern literatures, none of which cites him, have independently reconstructed his central claim — that the deposit's morphology and not its number determines the injury around it — and that one of them has restored, unknowingly, the exact simile he chose to describe it.

II. What Fischer Examined

Fischer's work is often summarised in a sentence, and the summary usually understates the material. The numbers are worth stating precisely, because the argument of this paper depends on the observations having been made at a scale that supports them.

The 1907 report. Fischer examined sixteen cases of senile dementia and found plaques in twelve [5]. The comparison groups matter as much as the cases: he found no plaques in ten non-demented controls, in ten cases of psychosis, or in forty-five cases of neurosyphilis. Neurosyphilis is the significant control, because general paresis was in 1907 the paradigm of an organic dementia with a known cause, and a lesion that appeared in senile dementia and not in general paresis was thereby established as specific to a syndrome rather than generic to brain disease. Of the twelve plaque-bearing cases, Fischer described the clinical picture as presbyophrenia — a form of dementia marked by confabulation, disorientation, memory impairment, hyperactivity and elevated mood. The paper appeared in the same year as Alzheimer's description of Auguste

Deter, on a cohort sixteen times the size, and it made the clinicopathological correlation Alzheimer's single case could not.

The 1910 monograph. The second study is the substantial one and is the source of everything that follows in this paper. Fischer examined two hundred and seventy-five brains drawn from cases of psychosis, neurosyphilis, and controls of various ages, of which one hundred and ten were from subjects over fifty at death [5]. He found plaques in fifty-six cases, all of them over fifty. Of those fifty-six, forty-two were clinically presbyophrenic and a further fourteen showed at least some presbyophrenic features. He recorded neurofibrillary tangles in seventeen per cent of the plaque-bearing cases. The monograph runs to approximately one hundred pages.

The 1912 consolidation. The third paper brought the total series of cases with both the morphological lesion and presbyophrenic dementia to seventy-two, of which twenty-one per cent also showed tangles [5]. Two findings in it deserve attention. First, Fischer identified ten cases out of forty-four in which presbyophrenic symptoms occurred in the setting of arteriosclerotic dementia *without* plaques, and named the condition arteriosclerotic pseudopresbyophrenia. This is a clinicopathological dissociation reported against his own thesis, and it is the mark of a careful investigator: he had a syndrome and a lesion he believed were joined, and he published the cases in which they came apart. Second, he examined thirty-five subjects aged sixty to ninety-three whom he regarded as normal and found plaques in only two, which he interpreted as presymptomatic disease.

That last figure requires a comment, because it is the one place where Fischer's numbers do not survive contact with modern series. Contemporary community-based autopsy studies find that on the order of a third of cognitively unimpaired elderly subjects meet pathological criteria for Alzheimer's disease [2]. Two of thirty-five is under six per cent. The discrepancy is almost certainly one of threshold and of stain rather than of population. Bielschowsky silver impregnation renders the fibrillar and neuritic components of the lesion visible; it is much less sensitive to the diffuse, non-fibrillar deposits that constitute the majority of the amyloid load in the cognitively normal elderly and that were not reliably demonstrable until immunohistochemistry. Fischer was scoring what would now be called neuritic plaques, in quantity. His specificity was bought with sensitivity, and the trade is visible in this number.

The methodological point generalises, and Fischer stated it himself at the opening of the 1910 monograph. The lesion, he wrote, is best demonstrated by Bielschowsky's method; with most of the staining methods then in use the relevant elements are either not coloured at all or so indistinct that they are easily overlooked, and this is why so frequent a change became known so late. It is a remark about the dependence of a lesion on the technique that reveals it, and we shall have occasion to return to it, because the same dependence is the live methodological controversy in the extracellular-matrix literature of the last five years.

Fischer's methodological discipline extended further than the choice of stain. He was aware that a newly described structure demonstrable by a single silver technique invites the suspicion of artefact, and he addressed it directly: he fixed his material in formol soon after death, cross-checked across a panel of stains — haematoxylin-eosin, van Gieson, Weigert's myelin and glial methods, polychrome methylene blue, tannin-methylene blue — and confirmed that the larger deposits were visible in unfixed fresh frozen sections, which no impregnation artefact could produce. He also ran the bacterial stains of the period, Gram and Ziehl-Neelsen among them, and reported them uniformly negative.

III. The Eight Types, and the Continuum of Five

The core of the 1910 monograph is a morphological classification. Fischer distinguished eight types of the lesion. He held the first five to form a continuum extending from early to late, and treated the last three as describing what becomes of the deposit rather than how it is built.

The scheme, in his terms, runs as follows.

Stage	Fischer's description	Character
I	Small irregular star — fine fibrillar elements of about two micrometres radiating from a point, without a centre	Formation
II	Morning star (*Morgenstern*) — larger, with the threads regularly and radially set	Formation
III	Spoke — radial elements growing out from the star and becoming massive; the surrounding tissue retracts and a halo appears	Formation
IV	Wheel — a peripheral halo with radial spokes linking a centre to the margin	Formation
V	Fibrous ball — the large mature deposit with a dense centre; nuclei and nuclear debris appear within the larger examples	Formation
VI	Infiltration and destruction of the vessel wall — perivascular deposits, and vessel walls infiltrated by what appears to be the same material	Fate
VII	Destruction of the deposit — the fibrillar structure loses integrity and the lesion dissolves	Fate
VIII	Diffuse infiltration of the nervous tissue by the material	Fate

Two features of this scheme are worth drawing out before the modern mapping is attempted, because both bear on how much weight the staging can carry.

The first is that the developmental claim — that stages I through V are one process observed at successive times — is an inference from cross-sectional post-mortem material, and Fischer knew it. He argued for it on three grounds: the existence of intermediate forms bridging each adjacent pair; the co-occurrence of the full range within single brains, in proportions that shifted with the severity of the case; and the fact that the club-shaped neurites, which are the process's most conspicuous secondary feature, appear only in the later members of the series. None of these is a demonstration. Together they are a reasonable argument for a temporal ordering, and it is the same argument, made from the same kind of material, that underlies Braak's staging of neurofibrillary pathology and Thal's phasing of amyloid deposition [9,10]. It is not a weaker foundation than the ones the field currently builds on; it is the same foundation.

The second is that stages VI, VII and VIII are not further steps along the continuum, and reading them as such — as though the lesion proceeded from a fibrous ball into a vessel wall and then dissolved and then infiltrated diffusely — misdescribes what Fischer proposed. They are three different things that can happen to a mature deposit, and they are not mutually exclusive or sequentially ordered. This matters for the mapping, because the modern correlates of the three are entirely distinct phenomena with distinct literatures: cerebral amyloid angiopathy, plaque clearance, and confluent late-stage deposition. Presenting Fischer as the author of an eight-step sequence obscures the structure of his own argument, which is a five-step formation and three fates.

A note on the naming. In 1907 Fischer called the lesion *drüsige Nekrose* — glandular or drusen necrosis — the adjective chosen for the radially organised, gland-like morphology and the noun for the necrotic appearance of the centre. By 1910 he had replaced it with *Sphaerotrichia multiplex cerebri*, from the Greek for sphere and for thread or hair, to capture what he took to be the lesion's essential character: a spherical formation of filaments. Neither term survived. The field kept "plaque," a word that describes a patch on a surface and carries no information about internal organisation, and after Divry appended "amyloid," a word that describes a staining property of the centre. The vocabulary the field adopted names the deposit's location and its core chemistry. Fischer's names both describe its architecture. Nomenclature is not usually load-bearing, but in this case the terms record what each generation thought the important fact about the object was, and the shift from architecture to chemistry is the shift this paper is about.

IV. The Neurite Finding

Among the observations in the 1910 monograph there is one that is more consequential than the staging that surrounds it, and it is very rarely quoted.

Fischer reported that club-shaped abnormal neurites were present in approximately fifty per cent of the plaques he examined. Of those that carried them, most were at stage V, some at stage

IV, and a few at stage III. Stages I and II carried none at all [5].

Consider what kind of result this is. It is not a between-subject comparison — not "demented brains have more damaged neurites than controls," which would be confounded by everything that differs between two people. It is a within-brain, per-object measurement: every plaque in a section is an independent observation, scored for two variables, morphology and neuritic injury, in the same tissue, in the same subject, under the same fixation and the same stain. The design controls for age, agonal state, post-mortem interval, fixation, disease duration and genotype by construction, because all of them are held constant across the objects being compared. It is the design that quantitative neuropathology now regards as the strongest available for questions of local pathology, and Fischer used it because it was the only way to establish a developmental ordering from static material.

The result has two components and both matter.

The first is that *half the plaques carried no neuritic injury at all*. This alone is sufficient to demonstrate that plaque number cannot be the correct measure of a plaque population's effect on the tissue around it, since half the objects being counted are not doing the thing the count is being used to infer. It is a refutation of the count made three-quarters of a century before the count's failure became a crisis, on the count's own material.

The second is that neuritic injury was *ordered by stage*. It was absent from the two earliest morphologies, appeared at the third, and was concentrated at the fourth and fifth. Injury was therefore not distributed randomly across the plaque population; it tracked a morphological variable that could be scored by eye. The variable that predicts damage was, in 1910, already known to be visible.

Fischer was also clear about what the club-shaped structures were. He identified them as neuronal, on the grounds of their staining behaviour and their fibrillar internal structure, and he compared their appearance to a phenomenon already familiar from a different experimental setting: the multiple subdivisions of the axon and the club-like swellings at the terminations of the fibrillary network seen with the Cajal and Bielschowsky silver methods after transection of a peripheral nerve. He was, in other words, reading them as a growth or injury response of neuronal processes, by analogy to regeneration after axotomy. The modern account of the dystrophic neurite is a good deal more specific — these are swollen axonal and dendritic endings, packed with LAMP1-positive lysosomal material deficient in cathepsins, enriched for BACE1, containing hyperphosphorylated tau, and constituting a site of local amyloid generation [11,12] — but the categorisation as an injured neuronal process reacting around the deposit is the same, and it was arrived at from morphology alone.

The finding that half of plaques are neuritically silent has a further consequence that Fischer did not draw and that the modern literature has. If the plaque population contains a benign majority

and an injurious minority, then a therapy that removes plaques indiscriminately removes mostly the benign ones, and the fraction of the burden it clears will overstate the fraction of the injury it prevents. We return to this in Section X, where the experiment has been done.

V. What Fischer Concluded, and What He Did Not

Fischer's interpretive claims should be separated from his observational ones, because they have had very different fates, and because a reading of his work has recently gained currency that his own conclusions do not support.

What he rejected. The dominant interpretation of the lesion when Fischer began was Redlich's: that the plaques were proliferated glial cells replacing dead neurons [13]. Fischer rejected it, and he rejected it on the strongest available grounds — not by argument but by staining. He reported that in preparations in which the glia were successfully impregnated he found neither glial fibres nor proliferated glial cells within or around the plaques, and he noted that Redlich had not stained the glia at all. Goedert's assessment of the historical record is unambiguous on this point: unlike Blocq, Marinesco and Redlich before him, Fischer did not believe in a glial origin of plaques [5]. He also rejected a bacterial aetiology, on the basis of uniformly negative Gram, Ziehl-Neelsen and related preparations.

The bacterial point requires a clarification, because it has been misread in both directions. Fischer described the mature lesion as resembling an actinomycotic granule — the radially organised, club-fringed colony that pathologists of the period knew well from actinomycosis of the jaw. Some later commentary has taken this as evidence that Fischer suspected a microbial cause and has enlisted him as a precursor of the infectious hypothesis. That is not what the text supports. He ran the bacterial stains, reported them negative, and used the actinomycosis reference as a morphological comparison — the only available vocabulary in 1907 for a spherical structure with a dense centre and a radiating, club-tipped periphery. The comparison was about shape. As Section VIII argues, it was also, for reasons Fischer could not have known, a better comparison than he intended.

What he concluded. Having removed the glial and bacterial readings, Fischer's positive account was cautious and, by the standards of his period, unusually restrained. He described the plaques as inclusions of unknown origin. In 1912 he stated the interpretation he had settled on: that the plaques were a proteinaceous metabolic product of the brain, rather than the debris of degenerating cells [5].

This conclusion should be read carefully, because it is the point at which a recently proposed reading of Fischer fails. It has been suggested that Fischer's descriptive language — his emphasis on the halo as a densification of the cortical ground substance, on the fibrillar and radial organisation of

the lesion, on the "thread" in *Sphaerotrichia* — amounts to an extracellular-matrix theory of Alzheimer's disease pathology, developed a century before the tools to test it existed and displaced by the amyloid framing that followed Divry. On that reading, the modern literature on the perineuronal net is a rediscovery of a founder document, and the twentieth century's concentration on the chemistry of the core was a wrong turn away from an available and better idea.

The reading does not survive Fischer's own summary. A matrix theory holds that the lesion is a rearrangement of material already present in the extracellular space. Fischer concluded the opposite: that the plaque is a metabolic product — something the brain makes and deposits, of unknown provenance, proteinaceous in character. That is a deposition theory. It is closer in structure to the amyloid framing than to the matrix one, and the identification of the amyloid-β peptide as a proteolytic product of a membrane protein, purified first from meningeal vessels in 1984 and then from plaque cores in 1985, substantially vindicated it [7,8]. Fischer got the general category right. Describing him as the founder of a matrix theory requires setting aside the one interpretive sentence he committed himself to.

There is a cost to the misreading beyond its inaccuracy, and it is the reason we spend a section on it rather than a footnote. Recruiting Fischer as a matrix theorist makes his actual contribution invisible. It directs attention to his adjectives — ground substance, filaments, threads — and away from his measurements, which are the staging and the stage-conditional distribution of neuritic injury. Those measurements are not a theory of what the plaque is made of. They are a claim about which variable predicts harm, and it is a claim the field can still use, because it is still, as Sections VI to XII will show, the claim the evidence supports.

What he did not have. It is equally important to be clear about the limits of what Fischer could see. He had no way to distinguish diffuse from fibrillar deposits by their protein content, no cellular taxonomy of the cortex beyond the morphological classes then available, no marker for microglia — Río-Hortega's identification of the cell was still a decade away — and therefore no way to know that the cellular nuclei he observed inside his larger deposits, which he took for entrapped and dying cells of the surrounding tissue, belonged to a population that had migrated to the deposit and was doing something to it. He had no biochemistry of the core. He had no means of following a lesion in time in a living brain. Everything in Fischer that has survived is morphology, and the argument of this paper is that this is not a limitation to be apologised for but the reason his record remains usable: morphology is the variable that the count discarded, and it is measurable now with instruments he would have recognised as doing his job better.

Part Two — The Stages Against the Modern Evidence

VI. Stages I and II The Uncompacted Deposit

Fischer's two earliest morphologies are small and simple: an irregular star of fine fibrillar elements about two micrometres across, radiating from a point without a defined centre; and a larger, regular version of the same in which the threads are set radially and evenly, which he called the morning star. Neither has a halo. Neither has a core. Critically, neither carries a single club-shaped neurite.

The modern correlate of these two forms is the deposit before compaction, and the correspondence is good but it is not exact, and the inexactness is instructive.

What the modern literature calls a diffuse plaque is a loose, non-fibrillar or weakly fibrillar accumulation of amyloid-β, predominantly the 42-residue species, which is negative or nearly negative for thioflavin-S and Congo red, has no dense centre, and — the point that matters here — is not associated with dystrophic neurites, reactive astrocytes or a microglial reaction [14]. Diffuse deposits constitute the majority of the amyloid load in cognitively unimpaired elderly subjects and are the earliest form to appear in the sequence of regional involvement that Thal and colleagues codified as phases one to five [10]. They are, in the plainest terms, the plaque that is not doing anything.

Fischer's stages I and II are the same claim about the same end of the sequence — a small deposit without a core and without neurites — but they are almost certainly not the same object. Bielschowsky silver impregnation demonstrates fibrillar material. It is relatively insensitive to the non-fibrillar diffuse deposit, which is why Fischer found plaques in only two of thirty-five elderly non-demented subjects where a modern immunohistochemical series would find them in roughly a third. His stage I is therefore best understood not as the first deposit but as the first *fibrillar* deposit — the earliest form his stain could see. There is a stage zero in front of it, invisible to him, and it is the most numerous form of all.

The claim that the diffuse deposit provokes no reaction at all should be stated with one qualification, because the boundary is not perfectly sharp. Lysosomal markers, including LAMP1, have been demonstrated in association with diffuse as well as neuritic plaques in the human hippocampus [12], which suggests that the transition from inert to injurious is graded rather than

categorical, and that some response to the deposit is present before the swollen argyrophilic profile that Fischer could see becomes visible. This does not disturb the ordering — the frank dystrophic neurite remains a feature of the later forms — but it means the earliest stages are better described as *below the threshold of visible injury* than as provoking nothing.

This is a genuine limitation of the scheme and it should be stated as one rather than argued around. It also has a consequence that runs in the scheme's favour. If Fischer's series begins one step downstream of the true beginning, then his finding that neuritic injury is absent from stages I and II is *conservative*: he established the absence of injury for the earliest fibrillar forms, and the still-earlier non-fibrillar forms are, on modern evidence, even more inert. The neuritically silent fraction of the plaque population is larger than Fischer's fifty per cent, not smaller.

The functional reading of these stages follows from what the deposit is not yet doing. In the in vivo imaging work of Condello and colleagues, new plaques appear and are then acted upon: microglial processes reach the nascent deposit and begin to envelop it, and the deposit's subsequent morphology depends on whether that reach succeeds [15]. Stages I and II are the interval before the outcome is decided. They are also, for that reason, the interval in which the deposit has not yet acquired the property that makes the later stages dangerous, which is a gradient.

VII. Stages III and IV — Compaction, and the Appearance of the Halo

At stage III something changes in Fischer's description, and the change is the pivot of the whole scheme. The radial elements grow out from the star and become massive; the surrounding tissue retracts; and — in his words, in translation — *a halo develops*. At stage IV the structure is complete: a peripheral halo, a centre, and radial spokes connecting them. This is the wheel.

Two things happen at this transition on Fischer's own data. The lesion acquires an internal architecture with a distinguishable centre and periphery, and the club-shaped neurites make their first appearance — a few at stage III, more at stage IV.

The modern account of this transition is the best-evidenced part of the entire mapping, and it was assembled by a route that had nothing to do with Fischer.

Condello, Yuan, Schain and Grutzendler, using high-resolution confocal and in vivo two-photon imaging in amyloid-depositing mice, showed that microglial processes form a physical barrier around the deposit, and that this barrier determines the deposit's local chemistry [15]. Plaque microregions covered by microglia are compact and show low affinity for Aβ42; microregions left uncovered show high Aβ42 affinity, and it is at these uncovered regions that protofibrillar Aβ42 hotspots form. The hotspots, in turn, are associated with more severe axonal

dystrophy. The barrier, in short, prevents outward expansion of the deposit and holds the neurotoxic protofibrillar species off the surrounding neuropil.

Read that result beside Fischer's stage III and the correspondence is close to literal. Fischer describes the tissue retracting and a halo appearing; the modern imaging describes a compacting core and a surrounding zone whose extent is set by how completely the deposit is covered. Fischer describes the neurites appearing at the moment the halo appears; the modern imaging describes the dystrophy tracking the protofibrillar hotspots that form where the covering fails. The halo is not a decorative feature of the lesion. It is the toxic gradient, and its extent is measurable.

The human demonstration comes from a genetic experiment that Fischer's scheme predicts the shape of. Yuan and colleagues examined mice haplodeficient for *Trem2* or *Dap12* and, decisively, post-mortem tissue from human carriers of the *TREM2* R47H variant [16]. Microglia in these tissues showed a markedly reduced ability to envelop amyloid deposits. The consequences were precisely stage-shaped: an increase in the number of less compact, filamentous deposits, and a greater extent of dystrophic axons and neuronal processes bearing hyperphosphorylated tau.

The importance of this result for the present argument is that it holds the count approximately fixed and moves the morphology. R47H carriers are not distinguished by having more plaques. They are distinguished by having plaques that have failed to complete Fischer's transition from stage II to stages IV and V — deposits arrested in a filamentous, uncompacted form — and by the severe neuritic injury that accompanies the arrest. In Fischer's vocabulary, the R47H brain is stage-shifted, and its dementia risk, roughly three- to four-and-a-half-fold across the reported series [17,18], is attached to the shift rather than to the burden.

This inverts an intuition that a count encourages. On a count-based reading, a compact dense-core plaque looks like the advanced and therefore the worst form, and the diffuse filamentous deposit looks like the early and therefore the milder one. On the containment reading, compaction is the *successful* outcome: it is what the tissue achieves when the response works, and the filamentous deposit is what remains when it does not. Fischer's stages III and IV are not a description of the lesion getting worse. They are a description of the tissue getting the lesion under control, and the neurites that appear alongside them are the price of a containment that is under way but not yet complete.

VIII. Stage V — The Mature Deposit, and the Cells Inside It

Stage V is the large, mature deposit: the fibrous ball with a dense centre, corresponding to what the modern literature calls the dense-core or cored plaque, thioflavin-S and Congo red positive, and — when it carries the surrounding halo of swollen neurites — the neuritic plaque that the CERAD protocol scores.

Fischer recorded one further observation about this stage which he could not interpret and which is, in hindsight, the most interesting sentence in the monograph. The smaller deposits, he wrote, are always cell-free; in the larger ones one finds nuclei or nuclear debris whose provenance is unclear, and certain intermediate images suggest that they are the remnants of cells which were enclosed by the growth of the deposit and thereby caused to perish.

He had the cells. He read the direction of causation backwards.

Río-Hortega's identification of microglia as a distinct cell population lay more than a decade in the future, and Fischer had no way to know that the nuclei inside his mature deposits belonged to a mononuclear phagocyte population that had migrated to the lesion and was actively building the structure he was looking at. He saw cells inside the deposit and concluded that the deposit had grown around and killed them. The modern account is that the cells came to the deposit, and that the deposit's dense, organised form is their work.

This brings us to the observation that motivated this paper.

In 2022 Lemke and Huang proposed, in the *Journal of Experimental Medicine*, that the dense-core plaques of Alzheimer's disease are granulomas — compact, organised collections of mononuclear phagocytes formed in response to a stimulus that cannot be resolved, of the same general class as the granulomas that macrophages assemble around *Mycobacterium tuberculosis* [19]. Their supporting observations are that microglia cover fifty to sixty per cent of the plaque surface at steady state; that depletion of microglia by CSF1R inhibition dramatically reduces plaque formation; that aggregated amyloid accumulates within the vesicular compartments of microglia, where the acidic environment promotes compaction; and that the transcriptional programme of plaque-associated microglia resembles that of macrophages within tuberculous granulomas. They draw an explicit therapeutic caution from the classification: if the dense-core plaque is a granuloma, simple disassembly of it may be inadvisable.

The comparison Fischer chose in 1907 was the granule of actinomycosis — the radially organised, club-fringed body that pathologists of the period knew from actinomycosis of the jaw, and from which the causal organism took its German name, *Strahlenpilz*, the ray fungus. He called the lesion *drüsige Nekrose* on the strength of that resemblance. The actinomycotic granule sits at the centre of a granulomatous lesion, and its distinctive morphology — a dense centre with a radiating, club-tipped periphery, walled off by the host from tissue it cannot clear — is the morphology of a containment structure. Fischer was not proposing that the plaque was infectious; he had run the bacterial stains and reported them negative, and he said the comparison was one of appearance. But the appearance he was matching to was the appearance of a granuloma, and one hundred and fifteen years later a paper arguing that the lesion belongs to that class was published without reference to him.

We do not present this as evidence for the granuloma classification, which stands or falls on the modern data. We present it as evidence about what morphology can do. Fischer had no biochemistry, no cell taxonomy and no immunology. He had a stain and a resemblance, and the resemblance he reached for encoded the organisational logic of the structure — walled, radial, built around something the tissue cannot dispose of — which is what a granuloma is. That the field spent a century treating this as a quaint nineteenth-century simile, and then arrived back at it by way of transcriptomics, is a fact about the information density of careful morphology.

One further modern finding bears directly on the contents of the mature deposit. Crapser and colleagues, examining human Alzheimer tissue, reported that aggrecan — the principal proteoglycan of the perineuronal extracellular matrix — is deposited within human dense-core plaques, demonstrating colocalisation of aggrecan signal within thioflavin-S-positive deposits [20]. The mature plaque, in other words, physically contains matrix material.

This deserves precise handling, because it is the one observation that could be enlisted to support the matrix reading of Fischer set aside in Section V, and it does not in fact support it. Fischer's descriptive claim was that the halo consists of the same ground substance as the surrounding cortex, more densely arranged — that is, that the matrix condensed in place. The modern finding is different: matrix material is present in the core, having been degraded elsewhere and incorporated, alongside evidence that the same microglia which build the deposit engulf perineuronal net material and that inclusions of net material are found within them [20]. Matrix ends up in the plaque. It does not get there by condensing; it gets there by being taken. The distinction is the difference between a rearrangement and a transport, and only the second is consistent with the cellular mechanism.

IX. Stage VI The Vessel, and the Direction of Travel

Fischer's sixth type describes perivascular deposits, and vessel walls infiltrated by what appears to be the same material, with resulting destruction of the wall [5]. He is describing cerebral amyloid angiopathy, in 1910, in the same monograph and with the same stain as the parenchymal lesion, and he is describing it as continuous with the parenchymal lesion rather than as a separate disease. Gustav Oppenheim described the vascular deposits independently the year before [21]. Neither made the connection to intracerebral haemorrhage that would later become the condition's principal clinical significance.

The mapping of this stage is the one where Fischer's causal reading is clearly wrong, and where the correction is more interesting than the error.

Fischer read the vessel involvement as invasion: the deposit, having matured in the parenchyma, extends into and destroys the vessel wall. The modern account runs in the opposite

direction along the same anatomical route. Amyloid-β is cleared from the brain's interstitium in part by drainage along the basement membranes of the cerebral vasculature, and cerebral amyloid angiopathy is understood as the deposition of the peptide within those walls when that drainage route fails or is overwhelmed. The parenchyma and the vessel wall are connected, as Fischer said, and the material is the same, as Fischer said. But the traffic is outward, and the lesion is a failure of removal rather than an act of destruction. What Fischer read as the deposit eating the vessel is the vessel silting up with material the parenchyma was trying to send out through it.

Two facts make this stage more than a historical correction.

The first is that the molecule which defines the modern disease was purified from Fischer's sixth stage rather than from his fifth. Glenner and Wong isolated and sequenced the amyloid protein in 1984 from cerebrovascular deposits — from meningeal vessels [7]. Masters and colleagues obtained it from plaque cores the following year [8]. The identity of the two established that the parenchymal and vascular lesions share a peptide, which is the molecular form of the continuity Fischer asserted on morphological grounds seventy-four years earlier. The stage he ranked sixth is where the material was first caught.

The second is that stage VI now governs the safety of the field's principal therapeutic strategy. Amyloid-related imaging abnormalities — the oedema and microhaemorrhage that constitute the dose-limiting toxicity of anti-amyloid monoclonal antibodies — arise from the vascular compartment, and their frequency and severity track the degree of cerebral amyloid angiopathy and *APOE* ε4 genotype. In Fischer's terms: the risk of attempting stage VII is set by the state of stage VI. It is difficult to think of a cleaner illustration that the morphological forms he separated are not taxonomic curiosities but distinct compartments with distinct behaviours, distinct clinical consequences, and — as the next section argues — distinct responses to being interfered with.

X. Stage VII The Dissolving Deposit, and the Experiment That Was Done

Fischer's seventh type is the deposit losing its integrity: the fibrillar threads coming apart, the structure dissolving. He treated it as one of the fates of a mature lesion rather than as a step in its construction, and he had no account of why it should happen.

Of the eight types, this is the one modern medicine has learned to produce on purpose, and the results are the most consequential test the staging scheme has been put to.

Active immunisation against Aβ42 in the AN1792 trial produced, in a subset of patients, clearance of amyloid plaques from the cortex — in some cases virtually complete removal. The long-term follow-up published by Holmes, Boche, Nicoll and colleagues in 2008 reported the

outcome: plaque clearance did not prevent progressive neurodegeneration [22]. Seven of the eight immunised patients who came to post-mortem assessment, including those with virtually complete plaque removal, had severe end-stage dementia before death, and there was no evidence of improved survival or of improvement in time to severe dementia against placebo. Follow-up at fourteen years found persistent neuropathological effects of the immunisation without a corresponding clinical benefit [23].

This is the count-based prediction and its refutation in the same experiment. If plaque burden were the pathogenic quantity, then removing the burden should arrest the process, and in patients in whom the burden was substantially removed the process continued to its end.

The staging scheme offers three readings of that failure, and they are not alternatives — they compound.

The intervention was applied at the wrong stage. By the time a patient meets criteria for Alzheimer's dementia, the plaque population is dominated by mature forms, and the neuritic injury Fischer observed at stages IV and V has already occurred. Removing the object does not restore the processes that swelled around it, any more than removing a splinter heals the wound. The deposit is not the injury; the deposit is the thing the injury happened next to.

Most of what was removed was not doing harm. Fischer's finding that half of plaques carry no neurites at all means that any therapy which clears plaques indiscriminately clears, in the main, the neutral majority. A treatment can therefore produce a large and genuine reduction in a measured quantity while producing a much smaller reduction in the injury that quantity was being used to represent. The dissociation between striking amyloid PET reductions and modest clinical effects in the current generation of passive immunotherapies has exactly this shape, and the staging scheme predicts it without needing to postulate that amyloid is irrelevant.

Dismantling a containment structure is not a neutral act. This is the sharpest of the three and it is the one Lemke and Huang state explicitly as a corollary of the granuloma classification [19]. If the dense core is a structure built to sequester material that cannot be cleared, then disassembling it returns that material to solution in the tissue. The imaging work of Condello and colleagues supplies the mechanism at the level of the individual deposit: it is the compact, covered plaque that has low protofibrillar Aβ42 affinity, and the uncovered regions that generate the neurotoxic hotspots [15]. A deposit taken apart is, transiently, a deposit with a great deal of uncovered surface.

We should be careful about how far to push this. The clinical trial record does not show that anti-amyloid therapy is harmful in the aggregate; the current agents show statistically significant, clinically modest slowing on the primary endpoints for which they were licensed. What it shows is that the magnitude of the clinical effect is very much smaller than the magnitude of the plaque

reduction, which is what a stage-based reading of the lesion predicts and a count-based reading does not. Fischer's seventh stage, produced deliberately, has told us that dissolving the deposit is not the same as undoing what the deposit's construction cost.

XI. Stage VIII — Diffuse Infiltration

The eighth type is the weakest member of the scheme and it should be labelled as such rather than mapped optimistically. Fischer describes a diffuse infiltration of the nervous tissue by the material of the deposit, associated with tissue destruction, and he treats it as a terminal fate. His description is brief and his examples few, and the passage in which he sets it out is partly concerned with the distinct question of whether the deposits in different cortical regions all develop at the same time.

Three modern phenomena are candidates for what he was seeing, and the available material does not adjudicate between them.

The first is confluent deposition: in advanced disease, dense-core and diffuse plaques become numerous enough that their halos overlap and the affected cortex reads as continuously involved rather than as a field of discrete objects. This is a real phenomenon at high burden and it matches the description.

The second is the diffuse, non-fibrillar amyloid that constitutes the majority of the cortical amyloid load and that Fischer's stain under-detected. If a subset of his cases carried enough of it to register faintly, he might have read it as material spreading out of the deposits rather than as a distinct deposit class. This is the reading we consider most likely, and it would make his stage VIII not a late fate at all but a partly-seen glimpse of the stage zero that stood in front of his stage I.

The third is the possibility that he was describing something outside the amyloid system altogether — the general tissue rarefaction of advanced disease, which he elsewhere described in a separate 1911 paper on spongy cortical atrophy as a distinct destructive process of the cortex.

We record stage VIII as unmapped. A staging scheme that fails to map one of its eight terms is in better condition than one that maps all eight by stretching, and it is worth noting that the term which fails is the one Fischer himself described most thinly.

XII. The Concordance, and What It Amounts To

The mapping can now be set out in one place.

Fischer's type	Fischer's description	Modern correlate	Principal evidence	Strength
— (**stage 0**)	Not visible with silver impregnation	Diffuse, non-fibrillar Aβ42 deposit; no core, no neuritic reaction	Thal phasing; immunohistochemical series in unimpaired elderly	Established; outside Fischer's record
I	Small irregular fibrillar star, no core, no neurites	Nascent fibrillar deposit before compaction	In vivo two-photon imaging of plaque appearance and microglial reach	Well supported
II	Morning star; larger, regularly radial; no neurites	Uncompacted fibrillar deposit; microglial envelopment incomplete	Condello 2015; Yuan 2016 (filamentous deposits in *TREM2* haplodeficiency)	Well supported
III	Spokes grow out; tissue retracts; **halo appears**; first neurites	Onset of compaction; protofibrillar halo established; dystrophy begins	Condello 2015 — uncovered microregions carry high-affinity Aβ42 hotspots and severe axonal dystrophy	Well supported
IV	Wheel — halo, centre, radial spokes; neurites frequent	Core-and-corona geometry of the compacted deposit	Condello 2015; Yuan 2016 human R47H autopsy tissue	Well supported
V	Fibrous ball with dense centre; **nuclei within larger examples**; neurites in ~50% of plaques overall, mostly here	Dense-core / neuritic plaque; mantle of plaque-associated microglia; granuloma classification; aggrecan incorporated in core	Lemke & Huang 2022; Crapser 2020; Serrano-Pozo 2016	Established for the structure; the granuloma classification is a proposal
VI	Perivascular deposit; vessel wall infiltrated and destroyed	Cerebral amyloid angiopathy — **direction of travel inverted**	Glenner & Wong 1984 (peptide purified from meningeal vessels); Oppenheim 1909; ARIA in anti-amyloid therapy	Established; Fischer's causal reading wrong
VII	Deposit loses integrity and dissolves	Plaque clearance; produced deliberately by immunotherapy	Holmes 2008 — near-complete removal, progression to severe dementia unaltered; Nicoll 2019	Established as an achievable state; its consequences argue against the count
VIII	Diffuse infiltration of the nervous tissue	Ambiguous — confluent deposition, under-detected diffuse amyloid, or non-amyloid rarefaction	—	**Unmapped**

Six of the eight map well; one maps with its direction reversed; one does not map. That is a serviceable record for a classification made with a single silver stain on formalin-fixed material more than a century ago, but the concordance is not, by itself, the argument of this paper. A morphological scheme can correspond to modern descriptions and still be a museum piece. What makes Fischer's scheme worth reviving is the quantitative claim attached to it, and that claim has now been reproduced with numbers.

Serrano-Pozo, Betensky, Frosch and Hyman examined dense-core plaques in temporal neocortex from forty subjects with Alzheimer's disease whose symptom duration ranged from four to twenty years, together with nine controls, and quantified the features surrounding each plaque [24]. They set out from the observation that plaque burden remains relatively stable across the clinical course, and asked whether the local toxicity of individual plaques changes even though their number does not.

It does. Dystrophic neurites, labelled with SMI312, rose significantly with symptom duration (Kendall $\tau = 0.34$, $P = 0.001$). Reactive astrocytes labelled with GFAP rose ($\tau = 0.30$, $P = 0.003$). CD68-positive microglia rose steeply ($\tau = 0.48$, $P < 0.0001$). IBA1-positive microglia did not change at all ($\tau = 0.045$, $P = 0.655$).

This is Fischer's finding at higher resolution and with a clock attached. The count is stationary; the stage advances. What accumulates over the twenty years of a clinical course is not more plaques but more injury per plaque, and the two variables come apart so completely that one is flat while the other rises across the entire observable range of the disease.

The IBA1 and CD68 dissociation in the same dataset is a second result of its own, and it bears on the reading of stage V. The number of microglia at the plaque does not change across two decades of disease; what changes is their lysosomal and phagocytic activation state. The cellular census of the containment structure is constant. What changes is what the cells in it are doing. Fischer's mature deposit is not a static object with a fixed cellular population; it is a structure of constant composition whose activity escalates, and it is the escalation, not the object, that tracks the clinical course.

Part Three — The Reading That Does Not Hold

XIII. The Distribution Data, and the Inversion

Fischer's 1910 monograph contains regional and laminar distribution data, and they have recently been enlisted in support of the matrix reading of his work set aside in Section V. The argument runs that his map of where the lesion occurs corresponds to the map of where perineuronal nets are concentrated, and that the correspondence identifies the object he was staging as a matrix lesion. The data do not support this, and the direction in which they fail is more informative than the claim they were recruited for.

Fischer reported the following. The deposits are found in the grey cortex and are most abundant in its upper layers, decreasing towards the deeper ones. They are absent from the white matter. They are absent from the other grey masses of the brain — he names the dorsal thalamus, the caudate and the lentiform nucleus — and from the cortex of the cerebellum, and he did not find them in the medulla. Across his series the frontal regions were more severely affected than the posterior in about half the cases, and in a small number the change was confined to the frontal lobe. The two hemispheres were generally affected symmetrically.

Now set that against what is known about the distribution of the perineuronal net in the human cortex.

Brückner and colleagues, in a systematic survey of human cortical areas published in 1999, found that neurons bearing perineuronal nets are most numerous in the primary motor cortex — approximately ten per cent of neurons in Brodmann's area 4 — and in the primary auditory cortex as a representative primary sensory area [25]. Their concentration is *lower* in secondary and higher-order association areas, and they are extremely rare in the entorhinal cortex.

That single sentence disposes of the correspondence claim. The entorhinal cortex is the region in which Alzheimer's neurofibrillary pathology is earliest and heaviest, and it is the region in which perineuronal nets are rarest. The primary sensory and motor cortices carry the highest net density in the brain, and they are the cortical regions involved last, or not at all, in the progression of the disease. If the lesion tracked net density, the disease would begin in the precentral gyrus and end in the entorhinal cortex, and it does the opposite.

Brückner and colleagues went further and asked the question directly. They found that the characteristic patterns of hyperphosphorylated tau largely *excluded* the zones abundant in perineuronal nets, and that neurons surrounded by nets were virtually unaffected by neurofibrillary tangle formation even in severely damaged regions [25]. Morawski and colleagues extended the same finding to the subcortex a decade later: the regions preferentially affected by tau — the basal nucleus of Meynert, the dorsal thalamus, the hypothalamic nuclei, the raphe nuclei and the locus coeruleus — are precisely those devoid of a characteristic aggrecan-based extracellular matrix, and in structures containing nuclei of differing tau severity, such as the amygdala, the thalamus and the oculomotor complex, the distributions of neurofibrillary tangles and of perineuronal nets are largely complementary [26].

Two conclusions follow, and they point in opposite directions from the one the matrix reading requires.

First, for tau, the net map and the pathology map are not a match but close to a negative image. This is a much better result for the perineuronal net than a match would have been, because it is what a *protective* structure should produce. A lesion appears where a defence is absent. That is the reading the net literature itself takes, and it is well supported.

Second, and more directly to the point, Fischer was not mapping tau. He was mapping his deposits, which are amyloid. Brückner's series addressed this too, and the answer is the flat one: the distribution of amyloid-β overlapped the proteoglycan-rich areas, but the patterns showed no precise correspondence [25]. Fischer's regional data are therefore neither a match to the net map nor its inverse. For the pathology he was actually looking at, the relationship is weak and unpatterned.

There is a real relationship between nets and plaques, but it lives at a different scale and it must not be conflated with the regional one. Crapser and colleagues, counting within human prefrontal cortex, found a nonlinear and highly significant inverse relationship between perineuronal net number and plaque count (Spearman $r = -0.49$, $P < 0.0001$), and showed in mouse models that depletion of microglia by CSF1R inhibition prevents net loss in 5xFAD animals despite persistent plaques and rescues nets in aged 3xTg-AD animals after a month of treatment [20]. Within a region, more plaques accompany fewer nets, and microglia are causally responsible for the net loss.

These are two different measurements and both are sound. Across regions, net-rich territory is pathology-poor, which is protection. Within a region, plaque-rich fields are net-poor, which is destruction. The first is a statement about where the disease goes; the second is a statement about what it does when it gets there. Reading either as licensing the claim that Fischer's deposit *is* a matrix lesion requires collapsing the two scales into one, and the regional data are unambiguous that they do not collapse.

XIV. Resilience Remodelling, Not Preservation

A second observation has been used to support the matrix reading, and it has been reported inaccurately often enough that it is worth stating what the source actually contains.

The study is de Vries, Bahnerth, Swaab, Verhaagen and Carulli's 2025 examination of perineuronal nets in cognitively resilient donors — individuals carrying Alzheimer-threshold amyloid and tau pathology who were not demented [27]. It is the closest look the field has taken at matrix biology in human resilience, and it is frequently summarised as showing that resilient brains preserve their perineuronal nets. It does not show that. It shows close to the opposite.

Aggrecan immunoreactivity around parvalbumin-positive neurons was *decreased* in resilient donors as well as in demented ones, significantly below controls ($P = .005$). Peridendritic net complexity was *reduced* ($P < .0001$). *Wisteria floribunda* agglutinin-positive net density was lower in the resilient group specifically, falling significantly below both the control and the demented groups ($P = .0005$). Tenascin-R was not measured at all; the term appears in the paper only inside a cited reference title. Synaptic contacts onto ensheathed neurons in resilient donors were a statistical null lying between the two comparison groups, not a demonstration of intactness. The authors' own framing of their headline result is perineuronal net *remodelling*, which they suggest may permit greater plasticity, and they are explicit that this is not preservation.

One element of the study does support a protective role for the matrix, and it should be given its due because it is the part most often omitted: excitatory neurons bearing a perineuronal net showed low amounts of phospho-tau [27]. That is the Brückner and Morawski finding reproduced at the level of the individual cell in resilient human tissue, and it is good evidence.

And one element supports a mechanism. Bulk transcriptomic gene-set enrichment showed the matrix-proteolytic programme — including *VCAN* and *ADAMTS2* — elevated in the demented group and not in the resilient one [27]. Both groups had fewer nets. Only one had the proteolytic signature.

This is the shape of a real result, and it is the same shape as Fischer's. In both cases a counted quantity fails to separate the groups, and what separates them is what accompanies the quantity. Resilient and demented brains both have fewer nets; the difference is whether the loss arrives with the proteolytic programme. Fischer's demented brains had many plaques, and so, as the twentieth century would discover, did many non-demented ones; the difference is whether the deposit has advanced through the stages at which it injures the neurites around it. In both cases the number is the wrong instrument and the accompaniment is the signal.

The parallel should not be pushed past what the evidence carries. The proposal that there are two distinguishable routes to a reduced net count — regulated remodelling and proteolytic

digestion, with different consequences — currently rests on a single bulk-transcriptomic contrast in one series. Cleavage-product neo-epitopes, the spatial relationship of net loss to nearby deposits, the fate of perisomatic synaptic contacts and the complement burden on them have not been scored in human tissue. Until they are, the two-route account is a hypothesis that rescues the resilience claim rather than a finding that establishes it.

XV. The Stain Problem, Twice

Fischer opened his 1910 monograph with a methodological observation. The change under consideration, he wrote, is best demonstrated by Bielschowsky's method; with most of the staining methods hitherto in use the elements in question are either not coloured at all or are so indistinct that they are very easily overlooked, and this is the reason why so frequent a change became known only so late.

He is describing a hazard that has recurred, in mirror image, in the modern literature on the same tissue.

Scarlett, Hu and Alonge argued in 2022 that the widely reported loss of perineuronal nets in Alzheimer's disease may be, in substantial part, a loss of *detection* rather than a loss of structure [28]. The reagent by which nets are most commonly visualised, *Wisteria floribunda* agglutinin, is a lectin: it binds a specific glycan configuration on the chondroitin-sulfate side chains, not the proteoglycan core. Their argument is that the diseased brain hypersulfates those chains, that hypersulfation alters lectin recognition, and that post-mortem Alzheimer tissue shows *increased* perineuronal net core protein expression alongside the changed sulfation pattern. On this account the net is not disappearing. It is changing its chemistry, and the standard reagent stops reporting it.

The two methodological situations are exact complements. In 1910 a real structure was invisible because no available reagent bound it, and a stain that did bind it revealed a lesion the field had been walking past for decades. In 2022 an apparent absence may be an artefact of a reagent that has stopped binding a structure which is still there. In both cases the object of study is defined by its stain, and in both cases the field's picture of the disease moved when the reagent did.

This bears directly on the resilience result of the previous section, and it bears on it in a way that is favourable to the part of that result which matters most. De Vries and colleagues measured net integrity two ways: with the WFA lectin, and with an antibody against aggrecan — that is, against the core protein [27]. The sulfation critique applies to the first measure and not to the second. The lectin result, in which resilient donors fell below both comparison groups, is the one most exposed to the objection, and it is also the one hardest to read as damage, since it is difficult to construct an account in which the non-demented group has sustained the most matrix destruction. The aggrecan result — decreased in resilient and demented donors alike relative to controls — survives the

objection, because an antibody against the core protein does not care how the side chains are sulfated.

The general lesson is one Fischer stated and the field has had to relearn: a lesion described by a single reagent is a claim about the reagent until it is corroborated by a second one that works on a different principle. It is the reason his own cross-checking across a panel of stains, and his confirmation of the deposits in unfixed frozen sections, was not fussiness. It was the argument.

XVI. Where the Matrix Does Belong

Nothing in the preceding three sections is an argument that the extracellular matrix is unimportant in Alzheimer's disease. It is an argument that the matrix is not the object Fischer staged, and that the two questions have been run together to the detriment of both. It is worth setting out, positively, what the matrix evidence does support, because the honest version is strong.

The matrix is a determinant of regional vulnerability. This is the best-supported matrix claim in the disease and it rests on independent human series a decade apart. Cortical areas rich in extracellular-matrix proteoglycans are less affected by the cytoskeletal pathology of the disease, and net-bearing neurons resist tangle formation even within severely affected regions [25]. The same holds subcortically: the nuclei preferentially attacked by tau are those without an aggrecan-based matrix, and within mixed structures the distributions of tangles and nets are complementary [26]. In resilient human tissue, net-bearing excitatory neurons carry low phospho-tau [27]. The net looks like armour, and the disease looks like something that goes where the armour is not.

The earliest site of the disease has no armour at all. The earliest hyperphosphorylated tau in the human brain appears in the locus coeruleus and the other subcortical aminergic nuclei, decades before symptoms; this temporal ordering is Braak's [9]. Those same nuclei are among the ones Morawski identified as devoid of the aggrecan-based matrix [26]. The two lines come from different series and should be cited together rather than merged, but read together they say that the disease starts in the least defended cells in the brain.

That fact bears on the scope of Fischer's scheme, and the bearing is a limitation. Fischer staged a cortical, amyloid, extracellular deposit. The earliest event in the disease's natural history, on the tau timeline, occurs in a small brainstem nucleus that carries none of his lesions at all, decades before his stage I appears anywhere in the cortex. A morphological staging of the plaque is a description of a late and downstream part of the process, however well it describes it, and no amount of concordance with modern plaque biology makes it a theory of onset. Fischer's own record contains the seed of this caution: he found tangles in seventeen per cent of his plaque cases in 1910 and twenty-one per cent in 1912, treated them as an accompaniment, and built his

classification around the deposit. The pathology that would turn out to track cognition most closely was the one he counted rather than staged.

The matrix is acted on by the same cells that build the deposit. Perineuronal net material is found within microglia in human Alzheimer tissue, aggrecan is deposited within human dense-core plaques, and depletion of microglia prevents net loss in mouse models even where plaques persist [20]. Whatever else is true, the cell that assembles Fischer's stage V is the cell that dismantles the net, and the two processes are therefore not independent. This is a genuine and mechanistically specific connection between the deposit and the matrix, and it is a connection through a shared effector rather than a shared identity.

The distinction that keeps all of this straight is between the deposit and the defences. Fischer staged the deposit and staged it well. The matrix literature describes the receiving neuron's defences and describes them well. Reading the second as a rediscovery of the first costs both: it makes Fischer's staging invisible, and it saddles the net literature with a claim about plaque composition that its own regional data contradict.

Prepared for Dr. James Truchard and Benjamin Gustafsson
Drafted by Claude-Opus-5
Synthesizing the work of Oskar Fischer

Part Four — Consequences

XVII. What the Count Cost

It would be unfair to say that the twentieth century abandoned Fischer's variable entirely, and the fairest account of what happened is more interesting than the caricature.

The CERAD protocol, which remains one of the three axes of the current neuropathological diagnosis, scores *neuritic* plaques specifically — deposits with dystrophic neurites around them — rather than all plaques indiscriminately. That is a partial stage measure. In selecting for the presence of the neurite it implicitly selects for Fischer's stages III to V and excludes his stages I and II, and it therefore carries forward, in a coarse form, the single most important thing he found. The field did not throw the stage away. It kept one bit of it.

But one bit is what it kept. The CERAD score is semiquantitative and it is categorical in the dimension that matters: a deposit either has neurites or it does not. It does not grade the compaction of the core, the extent of the halo, the completeness of the cellular mantle, or the severity of the dystrophy. It cannot distinguish a well-compacted deposit with a thin corona of a few swollen profiles from a filamentous, uncontained deposit surrounded by a wide field of them. Thal phasing, the second axis, is a distribution measure — where the deposits have reached — and is by design indifferent to what any individual deposit looks like. Neither instrument sees the variable that Yuan's *TREM2* series and Serrano-Pozo's duration series identify as the one that moves.

The cost is clearest at the point where the field spends the most money.

Amyloid positron emission tomography, the biomarker on which the modern therapeutic programme is built and against which its target engagement is judged, reports bulk fibrillar amyloid load. It is, functionally, a count with a weighting. It cannot distinguish a compact well-mantled deposit from a diffuse filamentous one; it weights the neutral majority of deposits equally with the injurious minority; and it registers the removal of a benign plaque exactly as it registers the removal of a malignant one. When such an instrument shows a large reduction and the clinical endpoint moves a little, the conventional readings are that the target was wrong or the timing was late. A third reading, which the staging scheme supplies, is that the instrument and the endpoint are measuring different quantities, and that a large movement in the first was never going to produce a proportionate movement in the second.

The sharpest illustration is genetic. *TREM2* R47H raises the risk of Alzheimer's disease roughly three- to four-and-a-half-fold [17,18] and does so, on the human autopsy evidence, without a corresponding increase in plaque burden — what it changes is deposit morphology and the neuritic injury around it [16]. A carrier and a non-carrier with the same plaque count have different diseases, and no count-based instrument, whether a neuropathologist's tally or a PET standardised uptake value ratio, can tell them apart. A biomarker that is blind to one of the strongest single-gene risk factors in the disease is not measuring the pathogenic variable. It is measuring something correlated with it, and the correlation is loose enough that half the objects being measured are not participating.

XVIII. An Operational Restatement of the Staging

If the argument to this point is correct, then the useful response is not to admire Fischer's scheme but to rebuild it with instruments that did not exist in 1910. What follows is a proposal, stated with enough specificity to be implemented and criticised.

The unit of measurement is the individual deposit, not the field and not the case. Four terms are scored per deposit, and each corresponds to something Fischer described.

Compaction. The ratio of dense-core area to total deposit area, by thioflavin-S or an equivalent amyloid-conformation stain. This is Fischer's distinction between the centre and the whole, and it is the term the *TREM2* literature moves.

Mantle coverage. The fraction of the deposit's perimeter, in a confocal optical section through its widest plane, in direct contact with microglial process membrane. IBA1 gives the most reliable post-mortem process label; a P2RY12 counter-stain is worth carrying, since plaque-associated cells characteristically lose the homeostatic checkpoint marker and the loss is itself informative. The denominator must be the deposit perimeter and not the area of the field, or the measure degenerates into a microgliosis score under another name. This is Fischer's observation of nuclei within the larger deposits, read in the direction he did not consider.

Halo extent. The radial distance, measured outward from the compact core, at which conformation-selective staining for protofibrillar and oligomeric species falls to background. This is Fischer's halo, and it is the term that carries the mechanism: coverage without halo extent is uninterpretable, because the claim is not that microglia surround deposits but that surrounding them shortens the toxic gradient [15].

Neuritic dystrophy. The area of SMI312- or LAMP1-positive dystrophic profiles within a fixed radius of the deposit margin, normalised to deposit perimeter. This is Fischer's club-shaped neurite, and it is the outcome the other three terms are being used to predict.

From these, a five-level index that recovers Fischer's continuum: **F0**, no core, no mantle, no dystrophy; **F1**, minimal compaction, partial mantle, no dystrophy; **F2**, established core with a measurable halo, mantle incomplete, dystrophy present but sparse; **F3**, compact core, extensive mantle, halo short, dystrophy moderate; **F4**, compact core, mantle breached or thin, halo wide, dystrophy severe. Note that F3 and F4 are not ordered by deposit maturity but by containment: the same mature deposit falls into one or the other according to whether its mantle is holding. This is the point at which the modern index departs from Fischer, and it departs because the mechanism is now known. He had one axis, and it was time. There are two, and the second is whether the response worked.

Three confounds must be matched across groups and reported, because they bear on these measures with particular force and each biases in a known direction. Agonal state and terminal illness alter microglial morphology. Post-mortem interval degrades fine process detail before it degrades somata, which biases the coverage term downward — that is, in the direction that flattens a true effect, so a null obtained without matching post-mortem interval should not be read as a null. Fixation duration alters conformation-selective epitope retrieval, which bears on the halo term.

Three uses follow immediately. The first is the decisive human measurement that has not been made: score the index in matched-pathology resilient and demented brains and regress it against antemortem cognition. The components have each been measured separately, and the second and third have been measured in human *TREM2*-variant tissue, but the full index has not been taken in matched resilient and demented material. The second is as a secondary endpoint in anti-amyloid trials, where it would separate a therapy that removes deposits from a therapy that improves their state. The third is stratification: a trial of an agent that acts on the containment response and does not stratify on the genotype of that response has left its own effect size to chance.

XIX. Predictions and Falsification

The argument makes claims that can be wrong, and each is attached here to the observation that would break it.

On the central claim. In human neocortex at matched plaque burden, per-deposit neuritic dystrophy will be predicted by compaction and mantle coverage, and the stage index will separate resilient from demented tissue more sharply than plaque count does. *Falsified if* dystrophy proves independent of deposit morphology at matched burden — that is, if the injurious and the benign plaques are morphologically indistinguishable.

On Fischer's fifty per cent. In unselected Alzheimer neocortex a substantial minority of thioflavin-positive deposits will carry no dystrophic neurite profiles at all, and the neuritically silent fraction will be stage-ordered, concentrated at the low-compaction end. *Falsified if* dystrophy is

present around essentially all fibrillar deposits, in which case the plaque population is homogeneous in the respect that matters and a count is the correct statistic after all.

On the genetic experiment. Formal staging of *TREM2* R47H autopsy tissue will show a distribution shifted toward the uncontained forms at equal deposit number, rather than a shift in deposit number. This is partly established already [16]; the prediction is that an explicit index reproduces it and that the shift, not the burden, tracks the clinical phenotype.

On the clock. Across symptom duration, the stage index will move and the count will not. The dystrophy and CD68 terms are established to move [24]; the prediction extends to compaction and halo extent, which have not been measured longitudinally in human material.

On therapy. Anti-amyloid immunotherapy will reduce deposit count by more than it reduces total stage-weighted burden, and the deposits remaining after treatment will be enriched for the higher-stage forms rather than representing a uniform thinning. *Falsified if* clearance proves stage-indifferent, which would mean the antibodies do not distinguish the objects that matter from the objects that do not — a result that would still be worth having, since it would explain the size of the clinical effect directly.

On the matrix reading. At matched regional plaque burden, perineuronal net density will not predict the stage distribution of the deposits. *Falsified if* net density does predict deposit morphology, in which case the two axes are more tightly coupled than Section XVI allows and the separation of the deposit from the defences is too clean.

XX. What This Scheme Does Not Cover

A staging scheme is a description of one lesion, and the boundaries should be stated plainly rather than left for a reader to discover.

It is not a theory of onset. Fischer staged a cortical, extracellular, amyloid deposit. The earliest hyperphosphorylated tau in the human brain appears in the locus coeruleus decades before symptoms and before any cortical deposit exists [9]. Whatever the staging of the plaque describes, it describes something downstream, and no degree of concordance with modern plaque biology converts it into an account of how the disease begins.

It is not a theory of the pathology that tracks cognition. Tangle burden and, more strongly, synapse loss correlate with cognitive severity better than amyloid measures of any kind [3]. Fischer counted his tangles — seventeen per cent of plaque cases in 1910, twenty-one per cent in 1912 — and staged his plaques. The scheme inherits that emphasis, and the emphasis is on the less prognostic of the two lesions.

It does not cover most dementia. A substantial fraction of dementia in community-based autopsy series is not attributable to Alzheimer neuropathological change of any grade, and a substantial fraction of individuals reaching the highest Braak stages are not demented at death [2,29]. A better instrument for grading the plaque improves the description of one pathway and leaves the population question where it was.

It has no in vivo form. Every term in the proposed index is a post-mortem measurement on fixed tissue. Amyloid PET reports bulk fibrillar load and has no morphological resolution; there is at present no imaging modality that reports compaction, mantle coverage or halo extent in a living brain. This is the most serious practical limitation of the proposal, and it means the index can validate or invalidate a therapeutic hypothesis at autopsy but cannot currently guide treatment in a patient.

One of Fischer's eight types does not map. Stage VIII is recorded in Section XI as unmapped, and we prefer to leave it so.

The granuloma classification is a proposal. Lemke and Huang's argument that the dense-core plaque belongs to the granuloma class is well motivated by the coverage, depletion and transcriptomic data they assemble [19], and it is not established. The historical observation of Section VIII — that Fischer's chosen simile encoded the same organisational logic — is a remark about morphology, not independent evidence for the classification.

Much of the containment evidence is murine. The barrier mechanism was established by in vivo imaging in mouse models [15]. The human arm consists of *TREM2*-variant autopsy material [16], the descriptive human series in Crapser [20], and the duration series in Serrano-Pozo [24]. The generalisation of the mechanism to sporadic human disease is an inference across these, and a reasonable one, but it is an inference.

XXI. Strength of Evidence

The claims made above are not of one weight. They are graded here on three levels: **established**, meaning directly evidenced in human tissue or by convergent human and animal data; **well supported**, meaning strong animal data with partial human corroboration; and **inference**, meaning a synthesis consistent with the evidence but not directly demonstrated.

Claim	Grade	Basis
Plaque burden is a poor predictor of dementia; a substantial fraction of unimpaired elders meet pathological criteria	Established	Katzman; Perez-Nievas; community autopsy series [1,2,4]

Claim	Grade	Basis
Synapse loss is the strongest neuropathological correlate of cognitive severity	Established	Terry [3]
Fischer distinguished eight plaque types, held I–V a continuum, and found club neurites in ~50% of plaques, almost all at stages IV–V and none at I–II	Established as a historical record	Fischer 1907, 1910, 1912, as assessed by Goedert [5]
Microglia form a barrier that compacts the deposit and limits protofibrillar Aβ42 at its margin; uncovered regions carry hotspots and severe axonal dystrophy	Established in mouse; well supported in human	Condello 2015 [15]; Yuan 2016 human R47H tissue [16]
TREM2 **haplodeficiency and R47H produce less compact, filamentous deposits with severe dystrophy and phospho-tau at unchanged plaque burden**	Established in human autopsy material	Yuan 2016 [16]
Per-plaque dystrophy and CD68 activation rise with symptom duration while plaque burden does not	Established	Serrano-Pozo 2016, n = 40, τ = 0.34 and 0.48 [24]
Plaque clearance by immunisation does not prevent progression to severe dementia	Established	Holmes 2008; Nicoll 2019 [22,23]
Cortical areas rich in matrix proteoglycans are less affected by cytoskeletal pathology; net-bearing neurons resist tangles	Established	Brückner 1999 [25]; Morawski 2010 [26]; de Vries 2025 (excitatory neurons) [27]
Amyloid distribution shows no precise correspondence with proteoglycan-rich territory	Established	Brückner 1999 [25]
Cognitive resilience is associated with net *remodelling*, **not preservation; aggrecan and WFA density fall in resilient donors**	Established for the measurements	de Vries 2025 [27]
Microglia causally drive perineuronal net loss; aggrecan is found within human dense-core plaques	Well supported (murine causation, human description)	Crapser 2020 [20]
Deposit morphology, not deposit number, is the variable that predicts local injury	Inference across the above, and the paper's central claim	Sections VII, VIII, XII
The dense-core plaque belongs to the granuloma class	Inference (proposal)	Lemke & Huang 2022 [19]
Reported perineuronal net loss partly reflects altered lectin recognition rather than degradation	Inference (active controversy)	Scarlett, Hu & Alonge 2022 [28]

Claim	Grade	Basis
Fischer's stages VI and VII correspond to CAA and to therapeutic plaque clearance, with the causal direction of VI inverted	Inference from the historical text against modern correlates	Sections IX, X
The proposed F0–F4 index will separate resilient from demented tissue better than plaque count	Untested prediction	Section XIX

XXII. Conclusion

Oskar Fischer described the senile plaque more thoroughly than anyone else of his generation, on a larger series, with better controls, and he described it in the only vocabulary available to him, which was morphology. He distinguished eight types, argued that five of them were one process caught at successive moments, and reported that the injury the lesion does to the tissue around it — the swollen, club-tipped neurites that are its visible cost — was absent from the two earliest forms, sparse at the third, and concentrated at the fourth and fifth. Half of the plaques he looked at were doing nothing at all.

The century that followed replaced this with a number. There were good reasons for it: the number was reproducible, it could be compared across laboratories, and the chemistry of the core turned out to be tractable in a way that morphology was not. But the number carried a hidden assumption, which is that the objects being tallied are interchangeable, and Fischer had already published the evidence that they are not.

Three modern literatures have now reconstructed his claim without reference to him. High-resolution imaging established that a microglial mantle compacts the deposit and holds the neurotoxic species off the surrounding neuropil, and that where the mantle fails the deposit is filamentous and the neurites are destroyed — a mechanism confirmed in human tissue by carriers of a risk variant whose plaque burden is unchanged and whose plaque morphology and neuritic injury are not. Quantitative neuropathology across two decades of clinical course established that plaque number is stationary while per-plaque dystrophy and microglial activation climb. And a reclassification of the dense-core plaque as a granuloma restored the comparison Fischer chose in 1907, when he named the lesion for its resemblance to the walled, radiating, club-fringed granule of actinomycosis, and warned in the same paper that this was a statement about shape and not about cause.

We have declined a reading of Fischer that would make him the founder of a matrix theory of the disease. He concluded that the plaque was a proteinaceous metabolic product of the brain, which the isolation of the amyloid peptide substantially vindicated, and the regional distribution

data that reading depends on point the other way: the cortical territories richest in matrix proteoglycans are those least affected by the disease's cytoskeletal pathology, and the amyloid deposits Fischer actually mapped show no precise correspondence with proteoglycan-rich territory at all. The matrix matters in this disease, and what it looks like is armour on the receiving neuron rather than the substance of the deposit. Both accounts are better for being kept apart.

What remains, and what we have tried to make usable, is a measurement. The four terms of the modern index proposed in Section XVIII — compaction, mantle coverage, halo extent, neuritic dystrophy — are Fischer's core, his cells within the deposit, his halo and his club-shaped neurite, expressed as quantities. Every one of them has been measured; none of them has been measured together, in the same human tissue, against antemortem cognition. That is a study, not a research programme, and it would settle whether the variable Fischer was using is better than the variable that replaced it.

There is a temptation, in writing about a scientist who was marginalised in his lifetime and died in a Nazi prison, to make the argument a restitution. It should not be. Fischer was wrong about the direction of the vascular lesion, wrong about the cells inside his mature deposits, unable to see the most numerous form of the pathology he was classifying, and silent on the region where the disease now appears to begin. The case for reading him is not that he was right. It is that he was measuring something the field stopped measuring, that the thing he was measuring is now known to be the thing that predicts the injury, and that a hundred and sixteen years later the instruments have finally caught up with the question he was asking.

References

Numerical statements about Fischer's series are sourced to Goedert's assessment of the primary literature (reference 5); Fischer's own four papers are listed at 30–33. Quotations from Fischer are given in English translation.

1. Katzman R, Terry R, DeTeresa R, Brown T, Davies P, Fuld P, Renbing X, Peck A. Clinical, pathological, and neurochemical changes in dementia: a subgroup with preserved mental status and numerous neocortical plaques. *Annals of Neurology*. 1988;23(2):138–144. DOI: 10.1002/ana.410230206

2. Schneider JA, Arvanitakis Z, Leurgans SE, Bennett DA. The neuropathology of probable Alzheimer disease and mild cognitive impairment. *Annals of Neurology*. 2009;66(2):200–208. DOI: 10.1002/ana.21706

3. Terry RD, Masliah E, Salmon DP, Butters N, DeTeresa R, Hill R, Hansen LA, Katzman R. Physical basis of cognitive alterations in Alzheimer's disease: synapse loss is the major correlate of cognitive impairment. *Annals of Neurology*. 1991;30(4):572–580. DOI: 10.1002/ana.410300410

4. Perez-Nievas BG, Stein TD, Tai H-C, Dols-Icardo O, Scotton TC, Barroeta-Espar I, Fernandez-Carballo L, de Munain EL, Perez J, Marquie M, Serrano-Pozo A, Frosch MP, Lowe V, Parisi JE, Petersen RC, Ikonomovic MD, López OL, Klunk W, Hyman BT, Gómez-Isla T. Dissecting phenotypic traits linked to human resilience to Alzheimer's pathology. *Brain*. 2013;136(8):2510–2526. DOI: 10.1093/brain/awt171

5. Goedert M. Oskar Fischer and the study of dementia. *Brain*. 2009;132(4):1102–1111. DOI: 10.1093/brain/awn256

6. Divry P. Étude histochimique des plaques séniles. *Journal Belge de Neurologie et de Psychiatrie*. 1927;27:643–657.

7. Glenner GG, Wong CW. Alzheimer's disease: initial report of the purification and characterization of a novel cerebrovascular amyloid protein. *Biochemical and Biophysical Research Communications*. 1984;120(3):885–890. DOI: 10.1016/S0006-291X(84)80190-4

8. Masters CL, Simms G, Weinman NA, Multhaup G, McDonald BL, Beyreuther K. Amyloid plaque core protein in Alzheimer disease and Down syndrome. *Proceedings of the National Academy of Sciences USA*. 1985;82(12):4245–4249. DOI: 10.1073/pnas.82.12.4245

9. Braak H, Braak E. Neuropathological stageing of Alzheimer-related changes. *Acta Neuropathologica*. 1991;82(4):239–259. DOI: 10.1007/BF00308809

10. Thal DR, Rüb U, Orantes M, Braak H. Phases of Aβ-deposition in the human brain and its relevance for the development of AD. *Neurology*. 2002;58(12):1791–1800. DOI: 10.1212/WNL.58.12.1791

11. Sadleir KR, Kandalepas PC, Buggia-Prévot V, Nicholson DA, Thinakaran G, Vassar R. Presynaptic dystrophic neurites surrounding amyloid plaques are sites of microtubule disruption, BACE1 elevation, and increased Aβ generation in Alzheimer's disease. *Acta Neuropathologica*. 2016;132(2):235–256. DOI: 10.1007/s00401-016-1558-9

12. Hassiotis S, Manavis J, Blumbergs PC, Hattersley KJ, Carosi JM, Kamei M, Sargeant TJ. Lysosomal LAMP1 immunoreactivity exists in both diffuse and neuritic amyloid plaques in the human hippocampus. *European Journal of Neuroscience*. 2018;47(9):1043–1053. DOI: 10.1111/ejn.13913

13. Redlich E. Ueber miliare Sklerosen der Hirnrinde bei seniler Atrophie. *Jahrbücher für Psychiatrie und Neurologie*. 1898;17:208–216.

14. DeTure MA, Dickson DW. The neuropathological diagnosis of Alzheimer's disease. *Molecular Neurodegeneration*. 2019;14(1):32. DOI: 10.1186/s13024-019-0333-5

15. Condello C, Yuan P, Schain A, Grutzendler J. Microglia constitute a barrier that prevents neurotoxic protofibrillar Aβ42 hotspots around plaques. *Nature Communications*. 2015;6:6176. DOI: 10.1038/ncomms7176

16. Yuan P, Condello C, Keene CD, Wang Y, Bird TD, Paul SM, Luo W, Colonna M, Baddeley D, Grutzendler J. TREM2 haplodeficiency in mice and humans impairs the microglia barrier function leading to decreased amyloid compaction and severe axonal dystrophy. *Neuron*. 2016;90(4):724–739. DOI: 10.1016/j.neuron.2016.05.003

17. Guerreiro R, Wojtas A, Bras J, Carrasquillo M, Rogaeva E, Majounie E, Cruchaga C, Sassi C, Kauwe JSK, Younkin S, Hazrati L, Collinge J, Pocock J, Lashley T, Williams J, Lambert J-C, Amouyel P, Goate A, Rademakers R, Morgan K, Powell J, St George-Hyslop P, Singleton A, Hardy J. TREM2 variants in Alzheimer's disease. *New England Journal of Medicine*. 2013;368(2):117–127. DOI: 10.1056/NEJMoa1211851

18. Jonsson T, Stefansson H, Steinberg S, Jonsdottir I, Jonsson PV, Snaedal J, Bjornsson S, Huttenlocher J, Levey AI, Lah JJ, Rujescu D, Hampel H, Giegling I, Andreassen OA, Engedal K, Ulstein I, Djurovic S, Ibrahim-Verbaas C, Hofman A, Ikram MA, van Duijn CM, Thorsteinsdottir U, Kong A, Stefansson K. Variant of TREM2 associated with the risk of Alzheimer's disease. *New England Journal of Medicine*. 2013;368(2):107–116. DOI:

10.1056/NEJMoa1211103

19. Lemke G, Huang Y. The dense-core plaques of Alzheimer's disease are granulomas. *Journal of Experimental Medicine*. 2022;219(8):e20212477. DOI: 10.1084/jem.20212477

20. Crapser JD, Spangenberg EE, Barahona RA, Arreola MA, Hohsfield LA, Green KN. Microglia facilitate loss of perineuronal nets in the Alzheimer's disease brain. *EBioMedicine*. 2020;58:102919. DOI: 10.1016/j.ebiom.2020.102919

21. Ness AM, Aiken J. Gustav Oppenheim (1882–1937) and the discovery of cerebral amyloid angiopathy. *The Neuroscientist*. 2025. DOI: 10.1177/10738584241251828

22. Holmes C, Boche D, Wilkinson D, Yadegarfar G, Hopkins V, Bayer A, Jones RW, Bullock R, Love S, Neal JW, Zotova E, Nicoll JAR. Long-term effects of Aβ42 immunisation in Alzheimer's disease: follow-up of a randomised, placebo-controlled phase I trial. *The Lancet*. 2008;372(9634):216–223. DOI: 10.1016/S0140-6736(08)61075-2

23. Nicoll JAR, Buckland GR, Harrison CH, Page A, Harris S, Love S, Neal JW, Holmes C, Boche D. Persistent neuropathological effects 14 years following amyloid-β immunization in Alzheimer's disease. *Brain*. 2019;142(7):2113–2126.

24. Serrano-Pozo A, Betensky RA, Frosch MP, Hyman BT. Plaque-associated local toxicity increases over the clinical course of Alzheimer disease. *The American Journal of Pathology*. 2016;186(2):375–384. DOI: 10.1016/j.ajpath.2015.10.010

25. Brückner G, Hausen D, Härtig W, Drlicek M, Arendt T, Brauer K. Cortical areas abundant in extracellular matrix chondroitin sulphate proteoglycans are less affected by cytoskeletal changes in Alzheimer's disease. *Neuroscience*. 1999;92(3):791–805. DOI: 10.1016/S0306-4522(99)00071-8

26. Morawski M, Brückner G, Jäger C, Seeger G, Arendt T. Neurons associated with aggrecan-based perineuronal nets are protected against tau pathology in subcortical regions in Alzheimer's disease. *Neuroscience*. 2010;169(3):1347–1363.

27. de Vries LE, Bahnerth A, Swaab DF, Verhaagen J, Carulli D. Resilience to Alzheimer's disease associates with alterations in perineuronal nets. *Alzheimer's & Dementia*. 2025;21(2):e14504. DOI: 10.1002/alz.14504

28. Scarlett JM, Hu SJ, Alonge KM. The "loss" of perineuronal nets in Alzheimer's disease: missing or hiding in plain sight? *Frontiers in Integrative Neuroscience*. 2022;16:896400. DOI: 10.3389/fnint.2022.896400

29. Boyle PA, Yu L, Leurgans SE, Wilson RS, Brookmeyer R, Schneider JA, Bennett DA. Attributable risk of Alzheimer's dementia attributed to age-related neuropathologies. *Annals of*

Neurology. 2019;85(1):114–124. DOI: 10.1002/ana.25380

30. Fischer O. Miliare Nekrosen mit drusigen Wucherungen der Neurofibrillen, eine regelmässige Veränderung der Hirnrinde bei seniler Demenz. *Monatsschrift für Psychiatrie und Neurologie*. 1907;22:361–372.

31. Fischer O. Die presbyophrene Demenz, deren anatomische Grundlage und klinische Abgrenzung. *Zeitschrift für die gesamte Neurologie und Psychiatrie*. 1910;3:371–471.

32. Fischer O. Der spongiöse Rindenschwund, ein besonderer Destruktionsprozess der Hirnrinde. *Zeitschrift für die gesamte Neurologie und Psychiatrie*. 1911;7:1–33.

33. Fischer O. Ein weiterer Beitrag zur Klinik und Pathologie der presbyophrenen Demenz. *Zeitschrift für die gesamte Neurologie und Psychiatrie*. 1912;12:99–135.

34. Alzheimer A. Über eine eigenartige Erkrankung der Hirnrinde. *Allgemeine Zeitschrift für Psychiatrie und psychisch-gerichtliche Medizin*. 1907;64:146–148.