
The Cases Without Plaques

Solomon Carter Fuller's 1911 audit, read beside Oskar Fischer's — the same controls, the same dissociation, and the fork in what a plaque in an intact brain means

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September 2026

Fischer built the comparison groups in 1907; Fuller rebuilt them in Massachusetts in 1911 and cites him doing it. Both found plaques in the aged who were never demented. Fischer called those brains presymptomatic. Fuller called them old. A century has come down on Fischer's side of that, and the audit is worth recovering on its own terms rather than as a discovery it never was.

Contents

1. Introduction

- 1.1 October 1911*
- 1.2 The laboratory and the training*
- 1.3 What this assessment asks*

2. The Prague Precedent

- 2.1 What Fischer had already built*
- 2.2 Fuller knew*
- 2.3 What was actually new in 1911*

3. The Design

- 3.1 Four cells*
- 3.2 What the material was*
- 3.3 Three limits*

4. The State of the Question in 1911

- 4.1 Nine accounts of one lesion*
- 4.2 The two Fischer entries, and a misprint*
- 4.3 Three positions, weighed honestly*

5. The Results

- 5.1 Prevalence*
- 5.2 Atrophy and arteriosclerosis dissociate in both directions*
- 5.3 §VI — dementia without plaques*
- 5.4 §VII — plaques without dementia*
- 5.5 §VIII — the competing-disease control*
- 5.6 The tangle association*
- 5.7 Regional distribution*
- 5.8 The three tables, and a discrepancy*

6. The Conclusion He Drew

7. The Fork

8. What Held

- 8.1 Non-specificity, at scale*
- 8.2 The lesion is not what correlates with the dementia*
- 8.3 Deposition and failed clearance — where the two men agree*
- 8.4 The regional and laminar detail*

9. What Did Not Hold

- 9.1 The ordering claim*
- 9.2 The continuum claim overreaches*
- 9.3 What the material could not support*

10. Why Neither Reading Took

- 10.1 Alzheimer is not the actor*
- 10.2 What happened to Fischer is not what happened to Fuller*
- 10.3 What the naming did*

11. Assessment

12. Conclusion

References

Primary sources cited by Fuller (1911)

Abstract

In October 1911 the *American Journal of Insanity* published a seventy-three-page study by Solomon Carter Fuller, pathologist at Westborough State Hospital in Massachusetts, on the miliary plaques found in the brains of the aged. Ninety-three brains: thirty-three elderly people who died insane, split by whether they carried plaques; six elderly people who died without psychosis; fifty younger people who died of other mental diseases. It concluded that plaques "cannot be considered as characteristic for any special form of mental disease," and that uncomplicated senile dementia "appears, therefore, to be only an intensification of alterations found in normal senium."

It is a careful, unusually well-controlled paper, and it has been almost entirely absent from the historiography. It also does not mean what a modern reader, encountering it cold, will assume it means. This assessment reads it against the century that followed and against the work it was written to test. Five conclusions follow.

First, the comparison design was not Fuller's innovation, and he does not claim it.

Oskar Fischer had built it four years earlier. Goedert's assessment of the 1907 *Miliare Nekrosen* records sixteen cases of senile dementia with twelve plaque-positive, set against ten non-demented controls, ten cases of psychosis and forty-five cases of neurosyphilis — all plaque-negative. That is the same architecture Fuller would use in 1911: a diseased group, a non-diseased aged group, and a competing-disease group. Fuller cites Fischer three times and describes his controls explicitly. The question Fuller was auditing was Fischer's question, posed with Fischer's method, on a series a third the size of Fischer's 1910 monograph.

Second, what Fuller genuinely added was one emphatic positive in the cell that mattered. Fischer's non-demented controls were plaque-negative in 1907, and in 1912 he found plaques in only two of thirty-five aged non-demented subjects. Fuller's Case XXXIV — a man of eighty, no psychosis — had plaques "in goodly number," most numerous in the hippocampus, with neurofibrillary change in Ammon's horn. That is the high-pathology intact brain, described in 1911. It is one case, and Fuller braces it with Oppenheim's and Simchowicz's rather than resting on it.

Third, and centrally: the two men saw nearly the same fact and read it in opposite directions, and the modern field took Fischer's reading, not Fuller's. Confronted with plaques in an aged brain without dementia, Fischer in 1912 called those cases *presymptomatic*. Fuller in 1911 called them an index of senile involution — ageing, not disease. The concept the field now operates is preclinical Alzheimer's disease, formalised by the NIA-AA workgroup in 2011, and underwritten by Jansen's estimate of a twenty- to thirty-year interval between amyloid positivity and dementia. That is Fischer's sentence with instruments attached. Fuller was right that the plaque is not diagnostic. Fischer was right about what the plaque in the intact brain signifies. Neither man held both halves.

Fourth, one of Fuller's findings failed, and instructively. He reported that well-developed neurofibrillary degeneration occurred only in brains that also bore plaques — eight of sixteen plaque cases, none of seventeen without. Braak's 2011 series contains fifty-eight brains with tau confined to the locus coeruleus and no cortical tau at all. Fuller's tangle survey was cortical and hippocampal; he did not cut where the process begins.

Fifth, on mechanism the two men converge, and it is the strongest thing in either paper. Both rejected the reading then dominant — that the plaque is proliferated glia replacing a dead neuron. Fuller argued from the abundance of plaques in the molecular layer and white matter, where cell bodies are not, that the lesion is a deposit of the products of pathological metabolism, with the surrounding glial and neural proliferation representing "attempts at elimination" that "do not appear successful." Fischer concluded in 1912 that the plaque is a proteinaceous metabolic product of the brain rather than the debris of degenerating cells. Two investigators, two languages, one deposition-and-failed-clearance model, both against the consensus of their moment.

The assessment states what Fuller established, what his material could not support, and what the record has done with each; reports two arithmetic slips in the original that appear not to have been noticed before; and declines two tempting readings — that the paper was buried because of who wrote it, and that its author was the man who got Alzheimer's disease right before anyone else. Neither survives the evidence. What survives is a good auditor, working four years downstream of a better morphologist, reaching the correct answer to the narrower question.

i. Introduction

1.1 October 1911

The paper opens the second number of volume LXVIII of the *American Journal of Insanity*, the organ of the American Medico-Psychological Association and, from 1921, the *American Journal of Psychiatry*. It runs from page 147 to page 219 and carries seventeen plates. A footnote records that it was presented in abstract at the association's sixty-seventh annual meeting in Denver, 19–22 June 1911.

The timing places it precisely, and the placement matters for reading it. Alzheimer's single case had been shown at Tübingen in November 1906 and published in 1907. Fischer's *Miliare Nekrosen*, on sixteen cases, appeared months later the same year. Fischer's monograph on 275 brains came in 1910. Kraepelin's eighth edition, which created the name *Alzheimersche Krankheit*, also came in 1910. Perusini's four cases were 1909; Simchowicz's monograph, Barrett's American series and Alzheimer's further case were all 1911. Fischer's clinical consolidation would follow in 1912.

Fuller is therefore writing four years into an argument, not at its opening. Everything he does is a response to positions already on the table, and the position he responds to most often is Fischer's.

1.2 The laboratory and the training

Two facts about the author bear on the reading.

The first is that he had been in Munich. Fuller was one of five research assistants selected by Alzheimer for the laboratory at the Royal Psychiatric Hospital, and he translated much of Alzheimer's work into English, including the Auguste Deter case (Mohammed, 2021). His methods section is a catalogue of the Munich bench: Bielschowsky's silver impregnation, Mann's eosin–methylene blue, fuchsin–light green, Mallory's phosphomolybdic hæmatoxylin — the last three, he notes, "as employed by Alzheimer" — Weigert's glia and myelin stains, Herxheimer's scarlet for fat, van Gieson, Heidenhain, Nissl's methylene blue. He is not an outsider attacking the tradition. He is working inside it, with its own instruments, on a question its own members had opened.

The second is the material. A state asylum pathologist in 1911 had access no university clinic could match: a large, continuous, unselected autopsy series of the aged insane. Fuller's thirty-three elderly cases came to autopsy at Westborough during 1909, 1910 and the first three months of 1911, with two exceptions from slides prepared five years earlier; his fifty younger subjects come from the previous six years of the same laboratory. The six non-psychotic elderly brains came from outside

— supplied, he records, by Dr F. B. Mallory from the autopsies of Boston City Hospital for 1909 and 1910. An asylum does not generate control brains. He had to go and get them.

1.3 What this assessment asks

Four questions organise what follows. What did the study establish, as distinct from what it concluded? What in it was new, given what had already been published in Prague? Where the two accounts diverge, which one did the subsequent century vindicate? And why did neither reading displace the one the field actually adopted?

2. The Prague Precedent

Any assessment of Fuller's 1911 paper that does not begin with Fischer will get its novelty wrong, and the temptation to get it wrong is considerable: the four-cell design looks startlingly modern, and a reader who meets it without the German-language context will take it for an invention. It was not one. Fuller knew it was not one, and said so.

2.1 What Fischer had already built

1907. *Miliare Nekrosen mit drüsigen Wucherungen der Neurofibrillen*. Goedert's assessment records sixteen cases of senile dementia, twelve of them plaque-positive — and, crucially, three comparison groups: ten non-demented controls, ten cases of psychosis, and forty-five cases of neurosyphilis, in none of which plaques were found (Goedert, 2009). Eighty-one brains. The neurosyphilis group is the sophisticated control, because general paresis was in 1907 the paradigm case of an organic dementia with a known cause; a lesion present in senile dementia and absent in general paresis is thereby shown to be specific to a syndrome rather than generic to brain disease.

Set that beside Fuller's structure. Fuller's §VII is a non-demented aged group. Fuller's §VIII is a competing-disease group of fifty, of which twenty-seven are general paresis and three cerebral lues. The architecture is the same, and the neurosyphilis control is the same control, for the same reason.

1910. *Die presbyophrene Demenz* — a monograph on 275 brains, plaques found in 56. Here Fischer did something Fuller never attempted: he distinguished eight morphological types of the lesion, argued that the first five formed a developmental continuum, and reported that the club-shaped abnormal neurites which are the plaque's visible injury to surrounding tissue appeared in roughly half the plaques he examined — almost entirely at the two latest stages, occasionally at the third, and never at the first or second (Goedert, 2009). That is a claim that neuritic injury is conditional on plaque *stage*, made per-lesion, with each brain as its own control.

1912. *Ein weiterer Beitrag zur Klinik und Pathologie der presbyophrenen Demenz*. Two findings bear directly here. Fischer identified ten cases out of forty-four in which presbyophrenic symptoms occurred in arteriosclerotic dementia *without* plaques, and named the condition arteriosclerotic pseudopresbyophrenia — a clinicopathological dissociation published against his own thesis. And he examined thirty-five subjects aged sixty to ninety-three whom he regarded as normal, found plaques in two, and interpreted those two as presymptomatic disease.

2.2 Fuller knew

This is not a reconstruction imposed from outside. Fuller's own historical section states it:

"Fischer (1907) employing Bielschowsky's neurofibril method in a series of observations on the cortex of senile dementia and other psychoses could find the characteristic plaques in senile dementia only."

And, of the second report:

"Later (1908), after having studied 37 cases of senile dementia, 50 cases of paralytic dementia and 23 cases of other psychoses, Fischer was still unable to find plaques in cases other than presbyophrenia."

Fuller understood perfectly that Fischer had run controls, across diseases, at scale. His references list Fischer three times — the 1907 *Miliare Nekrosen*, the presbyophrenia *Sitzungsbericht*, and the 1910 *Die presbyophrene Demenz*. Fischer is the most-discussed investigator in Fuller's review, and the paper's design is legible as what it is: a replication of Fischer's test, in English, on American asylum material, by a pathologist who expected a different answer in one cell.

2.3 What was actually new in 1911

Three things, and they are narrower than the design.

An emphatic positive in the non-demented cell. Fischer's ten non-demented controls in 1907 were plaque-negative; his thirty-five in 1912 yielded two. Fuller's Case XXXIV yielded plaques "in goodly number" across four sampled regions, hippocampus-predominant, with neurofibrillary change in Ammon's horn. Where Fischer's non-demented brains were a near-clean negative, Fuller's single positive was unambiguous and heavy.

Both dissociation arms in one series, in one language, at once. Fischer's demented-without-plaques cases are in the 1912 paper; his non-demented series is in the same paper; his competing-disease controls are in 1907. Fuller has all of them inside a single study of ninety-three brains, tabulated together. That is a presentational rather than an evidential achievement, but presentation is not nothing: the four cells are visible on his contents page.

The English-language record. Before Fuller, the entire comparison literature was German. Barrett's 1911 series, which Fuller cites and which appeared in the same journal a volume earlier, had eight elderly cases and no control groups. Fuller's is the first substantial controlled series on this question in English.

None of this amounts to priority, and Fuller does not claim it. He opens by saying the literature "is not extensive," that the structures have been "studied intensively and with illuminating results" within the last three years, and that his object is "to add to already existing clinical and anatomical data."

3. The Design

3.1 Four cells

	Died insane	Died without psychosis
Plaques present	§V — 16 cases	§VII — Case XXXIV
Plaques absent	§VI — 17 cases	§VII — 5 cases

Beneath it, §VIII: fifty younger subjects dying of various mental diseases, examined by the same methods.

3.2 What the material was

The groups are unequal, and Fuller says so.

The thirty-three elderly insane are whole brains, examined systematically, with clinical histories from the hospital record. Fuller states that "the deductions noted at the end of this paper have been drawn chiefly from the study of the 33 elderly subjects dying insane."

The six non-psychotic elderly are not whole brains. They are "small pieces of brain fixed in formalin" from Boston City Hospital autopsies. For Case XXXIV, blocks were available from four regions: a six-layer cortex, probably frontal; anterior central cortex; corpus striatum; hippocampus. For the other five, in which he found none, the sampling is thin enough that absence is weak evidence — and he concedes it: "Material from elderly subjects without psychosis was limited." §VII establishes the *existence* of the plaque-positive non-demented brain. It does not estimate its frequency.

The fifty younger subjects are re-examinations of neurofibril slides already on file, plus four additional cases, bringing the total to ninety-three.

3.3 Three limits

It is cross-sectional; each subject contributes one time point, and no statement about sequence follows except by inference across ages.

It has no measure of cognition beyond an asylum's clinical record. "Dying without psychosis" means not committed and not recorded as insane. It does not mean cognitively assessed.

And it inherits a stain ceiling that matters more than it appears to. Fuller reports that "no case which failed to show plaques by Bielschowsky method revealed these structures by the other methods employed." Bielschowsky silver demonstrates fibrillar material and is relatively insensitive to the diffuse, non-fibrillar deposit that constitutes most of the amyloid load in cognitively normal elderly brains and was not reliably demonstrable before immunohistochemistry. Fuller — like Fischer — was scoring what would now be called neuritic plaques. His seventeen "non-plaque" brains are brains without *neuritic* plaques. Some of them almost certainly carried diffuse deposits neither man could see.

4. The State of the Question in 1911

4.1 Nine accounts of one lesion

Fuller's contents page lists nine standing explanations under "Historical":

- origin from degenerating ganglion cells
- glial encapsulation of amyloid and other bodies
- deposited products of pathological metabolism
- glia rosettes
- necrotic foci with proliferation of axis cylinders
- bacterial nature
- *Spirotrichia multiplex cerebri*
- circumscribed necroses of glial and nervous elements
- an index of senile involution

Redlich (1898) and Cramer (1904) held the first; Blocq and Marinesco had described the lesion in 1892. Mijake (1906) called them glia rosettes. Alzheimer, in his 1906 preliminary report, took the third — deposits of chemical substances from the pathological metabolism of nervous elements, which he called *Aufbau Produkte*. Wada held they were circumscribed necroses. Perusini (1909) offered a synthesis: degeneration of nervous elements, deposition of metabolic products in the thickened glial reticulum, and glial fibre proliferation seeking "to encapsulate the focus" as around a foreign body.

That *amyloid* is already present as a word in 1911 is worth a moment. It is Virchow's term, used here for the corpora amylacea and for whatever the glia was encapsulating — sixteen years before Divry's Congo red work.

4.2 The two Fischer entries, and a misprint

Entries six and seven belong to Fischer, and both require care.

On the bacterial question Fuller writes that in Fischer's later report "the opinion as to the nature of the plaques (necrotic foci surrounded by club-like proliferations of axis cylinders) was modified

and a bacterial origin was argued." He then rejects it — on the ground that it "has not been substantiated by subsequent observers," and that his own material does not support it.

This characterisation should be flagged rather than repeated, because the modern reading of Fischer contradicts it. Goedert records that Fischer rejected a bacterial aetiology on the basis of uniformly negative Gram, Ziehl–Neelsen and related preparations, and that his comparison of the mature lesion to an actinomycotic granule — the radially organised, club-fringed colony familiar from actinomycosis of the jaw — was a statement about *shape*, the only vocabulary available in 1907 for a spherical structure with a dense centre and a radiating, club-tipped periphery (Goedert, 2009). Fuller may be reporting a position Fischer entertained and abandoned, or he may be reading the morphological comparison as an aetiological claim. The published record as now assessed does not support attributing a bacterial theory to Fischer, and a reader coming to Fuller's summary should not take it as one.

The seventh entry compounds the problem typographically. Fuller's body text has Fischer designating the plaques "*sphaerotrichia multiplex cerebri*," emphasising that "the fibrillary components of the plaques are the most characteristic and important." The contents page prints *Spirotrichia*. Fischer's coinage was *Sphaerotrichia* — "spherical hair," for the radiating fibrillary organisation. The contents-page form invites a false reading, since *Spirotrichia* suggests a spirochaete and therefore an infection. It is a misprint, and the two entries should be understood as one investigator's morphological vocabulary and one investigator's disputed aetiological aside, not as two independent theories of the plaque.

4.3 Three positions, weighed honestly

By 1911 the specificity question had three answers, and Fuller's own review lets us see what stood behind each.

A specific new entity, named. Alzheimer's case of 1906–07, his further case of 1911, and Perusini's four of 1909: roughly six brains. Kraepelin had named it in 1910. Fuller notes drily that Alzheimer's 1911 case is "an example of 'Alzheimer's disease' described in the 8th edition of Kraepelin's Clinical Psychiatry," and adds that in this case "the peculiar type of intracellular neurofibril degeneration, however, was not present."

A specific lesion, bounded by controls. Fischer's. It is important not to caricature this as the naive position. Fischer's claim — that the plaque was the anatomical substratum of presbyophrenia — was tested against non-demented, psychotic and neurosyphilitic comparison groups in 1907, extended over 275 brains in 1910, and *qualified by Fischer himself* in 1912 when he found and named the cases where presbyophrenic symptoms occurred without plaques. This is a specificity claim held to account by its own author.

An index of senile involution. Huebner's 32 cases (1909), whose conclusion Fuller quotes: "the presence of miliary plaques in the brain is not characteristic for any special psychosis; that the subject had at least reached the 5th decade is the most that could be medico-legally advocated." Simchowicz's 108 brains (1911), for whom "the difference between normal senium and senile dementia is but a difference in degree." Oppenheim's non-psychotic man of 77 with abundant plaques. And Fuller's 93.

The asymmetry worth noting is not between Fuller and Fischer, who between them had examined well over four hundred brains and disagreed about interpretation. It is that the position which acquired the name — and through the name, the century — had been tested on about six.

5. The Results

5.1 Prevalence

Of the 33 elderly subjects dying insane, 16 — 48.48% — had plaques. Seventeen did not.

5.2 Atrophy and arteriosclerosis dissociate in both directions

Twenty-six brains were atrophic; eleven of those had plaques (42.3%). Seven were within the accepted normal range — he takes 1358 g for men, 1235 g for women — and five of those had plaques.

The printed text says "57 per cent of the normal-weight brains exhibited plaques," which is four of seven, not five. Five is the figure the rest of the paper requires: eleven atrophic plaque-brains plus five normal-weight ones give the sixteen he reports throughout. The percentage is the slip; the correct rate is 71%.

The two most atrophic brains in the series, at 821.1 g and 900.1 g, had none. His conclusion — "plaques cannot be predicated from atrophy alone" — is well supported, and he is properly cautious about the apparent reversal, warning that "a predisposition in favor of normal-weight brains, however, must not be assumed, for the reason that the cases are too few."

On vascular disease he is blunter. Not one of the 33 brains was free of macroscopic arteriosclerosis. Ten of the 16 plaque brains (62.5%) had gross focal lesions of arteriosclerotic origin — but arteriosclerosis "was even more pronounced in non-plaque brains," and the seven most typically arteriosclerotic cases sit in the non-plaque group. His conclusion: "Arteriosclerosis per se, therefore, appears to have little, if any, direct causative relationship to the formation of plaques."

He could not predict the finding from the autopsy table: "many brains in which, judging from gross anatomical findings and the clinical course as well, one might reasonably expect to find plaques, proved disappointing, while frequently some of the least suspected subjects were the most fruitful in their yield."

5.3 §VI — dementia without plaques

Seventeen cases. Seven fall clearly into arteriosclerotic insanity and show wedge-shaped cortical destruction. The crucial sentence concerns the others:

"certain non-plaque cases which coursed clinically as senile dementia did not show histologically, except by absence of plaques, lesions essentially different from the plaque cases."

Three of the seventeen are histologically indistinguishable from the plaque group once focal lesions are set aside. And the traffic runs both ways: one plaque case shows the wedge-shaped destruction characteristic of the arteriosclerotic group.

This is the same observation Fischer would publish a year later as arteriosclerotic pseudopresbyophrenia — reached independently, from the other side of the argument, and reported by both men against their own preferences.

5.4 §VII — plaques without dementia

Case XXXIV. A man of eighty, no psychosis, dying with pulmonary tuberculosis, chronic appendicitis, hydrocele and cerebral oedema.

"In sections from all of the blocks of tissue plaques were found in goodly number, but most numerous in sections from the hippocampal region. Alzheimer's intracellular degeneration of neurofibrils was seen in some cells of the large pyramidal layer, of Ammon's horn, missed in the other regions studied."

The general histology was "essentially those as appeared in cases of senile dementia reported in this paper," and in §X "essentially the same as those of the plaque cases, though of less intensity."

Fuller places the case in company: "Case XXXIV of this series, the case of Oppenheim, and cases reported by Simchowicz indicate clearly that plaques may be present without psychosis."

5.5 §VIII — the competing-disease control

Fifty younger subjects: 27 general paresis, 8 microcephalic idiocy, 5 chronic alcoholism, 4 manic-depressive insanity, 4 dementia præcox, 3 cerebral lues, 2 tuberculous meningitis, 2 brain tumour, one purulent meningitis, one psychosis with diffuse cord degeneration, one marked cerebral arteriosclerosis. Four older additions: a manic-depressive of 60, general paretics of 68 and 65, and a woman of 76 hospitalised over forty years.

"None of the cases in this group exhibited plaques."

He excludes two near-misses with discrimination. In the arteriosclerotic woman dying of lenticular hæmorrhage, and in a luetic case of 31 with multiple gummata, he found fibre-forming glia and lipoid-laden macrophages at the lesion periphery — "These cell colonies, however, were not the plaques with which we are concerned in this paper." Bickel had described just such collections as a variety of plaque; Fuller declines the identification.

5.6 The tangle association

"Well-developed Alzheimer degeneration of neurofibrils was found only in brains showing plaques."

Eight of sixteen plaque cases; none of seventeen non-plaque cases. Within the plaque cases, small and medium pyramidal furnished most examples, then the fusiform layer; in three cases all cortical laminæ were affected, particularly frontally; in another three, affected cells appeared only in the cornu Ammonis.

He also records, in a manic-depressive of 55 from the supplementary group, cells he reads as "possibly an early stage in the process which leads to the peculiar whirl-like and snarled arrangement in the typical late stage" — a pre-tangle, in a plaque-free brain, in the sixth decade. And he notes Simchowicz's *argentophile bodies* in the large pyramids of Ammon's horn: small homogeneous bodies surrounded by clear spaces, more numerous in cells from which neurofibrils have disappeared. That is granulovacuolar degeneration.

5.7 Regional distribution

"The frontal lobes and the hippocampal regions display the greatest richness in plaques. Precisely these are the regions which show generally the most advanced and most extensive histological lesions in the brains of aged persons, whether dying insane or not."

Occipital cortex generally showed fewest. Plaques were found in basal ganglia, cerebral white matter, brain stem and medulla. In cerebellum, no typical plaques. In spinal cord, none, though cords were not available for every case.

Stratigraphically, "no cortical layer appears immune"; where sparse they sit in the small and medium pyramidal layers, but in severe cases "an unbroken array of plaques extending from just beneath the pia, throughout all the cortical laminæ, deep into the white substance could be demonstrated." And: "the portion of convolutions forming the lips of sulci show more plaques as a rule than the summit area."

Case IX is the anomaly he reports rather than smooths: plaques confined to left prefrontal and left hippocampal regions, in a brain whose corresponding right-sided regions were otherwise indistinguishable.

5.8 The three tables, and a discrepancy

Recovered from the printed page — the microfilm text layer drops all three:

Decade	All 33 (Table I)	Plaque cases (Table II)	Non-plaque cases (Table III)
6th	3	1	—
7th	11	3	7
8th	10	6	7
9th	9	6	3
Total	33	16	17

The totals reconcile: $16 + 17 = 33$. The decade rows do not. Summing Tables II and III gives 1, 10, 13, 9 against Table I's 3, 11, 10, 9.

The likely source is a decade-assignment slip. Fuller states that three of his cases fell outside senium proper, aged 56, 59 and 60, and those three are almost certainly Table I's sixth-decade entry; the boundary case at 60 appears to have been counted differently between tables. With the normal-weight percentage of §5.2, it is one of two arithmetic slips in a paper whose case-level bookkeeping is otherwise sound: the counts reconcile everywhere it matters, and only the derived percentages and the decade rows wobble.

It does constrain what can be read out. It is tempting to derive an age-prevalence curve from Table II over Table I and report a rise from a third to two-thirds across the decades. The denominators will not carry it. What survives is the shape of Table III: non-plaque cases concentrated in the younger decades, plaque cases in the older. Plaque frequency rises with age in this material; the precise gradient does not follow.

6. The Conclusion He Drew

Section XI states ten numbered results. Four carry the argument.

(4) — the non-specificity finding:

"Since plaques have been found in the brains of elderly persons dying insane and in the brains of elderly persons dying without psychosis, and also as recorded in the cases of a young tabetic without psychosis, these peculiar structures cannot be considered as characteristic for any special form of mental disease, although occurring with greater frequency in senile dementia than in any other form of insanity."

The second clause matters. He does not claim the plaque is irrelevant; he claims it is not diagnostic, while conceding enrichment in senile dementia. That is the careful version, and it is the version the modern data support.

(5) and (6) — variation, and the reserved category:

"The onset of senile involution varies in different persons and this may explain the presence of plaques in the brains of some elderly persons and their absence in others."

"From the evidence furnished by Case XV of this series and the published cases of Alzheimer and Perusini, a precocious senium is conceivable. By precocious senium something more than an early cerebral arteriosclerosis is meant."

Fuller did not deny that Alzheimer had found something. He relocated it: ageing arriving early, and explicitly not reducible to early vascular disease.

(8) — the mechanism:

"The presence of plaques in the molecular layer of the cortex and in the white substance, often in great numbers, leads the writer to contend against an origin from degenerating ganglion cells. The view of deposited products of pathological metabolism resulting from degenerating nervous elements (fibrils) is advocated. The glial and also the apparently incontrovertible neural proliferations are interpreted as attempts at elimination of the deposited products. These attempts at elimination and replacement, nevertheless, do not appear successful."

The argument is anatomical and good. If plaques were the residue of dead neurons they should sit where neurons sit; instead they are abundant in layer I and white matter, "and this too without the slightest evidence of a heterotropia of the stratigraphy of ganglion cells." Ganglion cells found within or at the edge of plaques are often "in a fair state of preservation," and most plaques show no

affiliation with a cell body at all.

(10) — the nosological conclusion:

"Uncomplicated senile dementia, on histological grounds, appears, therefore, to be only an intensification of alterations found in normal senium."

He places himself in company: Robertson, Carrier, Alzheimer, Frankhauser and Simchowicz on the continuum side, against Siemerling, Appledorn, Fischer and Léri, who "conceive special pathological factors in addition to the normal alterations of senium, although the conception of these pathological factors are not definitely formulated."

Note who is on which side of that sentence. On the continuum side, Fuller lists Alzheimer. On the special-factors side, he lists Fischer. The alignment the modern reader expects — Alzheimer the disease-maker, Fischer the ageing-continuum man — is the reverse of how Fuller, writing in 1911 with both men's work in front of him, understood the field.

7. The Fork

Here is the pivot of the whole comparison, and it is a genuine disagreement about the same observation.

Both men found plaques in the brains of aged people who had not been demented. Fischer found them in two of thirty-five in 1912. Fuller found them, abundantly, in one of six in 1911. Neither result is large. Both are real.

Fischer called those cases presymptomatic. On his reading, the person carried the disease and had not yet shown it. The lesion was an early stage of a graded pathological process with a clinical destination.

Fuller called them an index of senile involution. On his reading, the person was simply old, the brain had aged, and the lesion belonged to ageing rather than to any disease. Hence conclusion (10): senile dementia as an intensification of normal senium.

These are not compatible, and the century has adjudicated.

The framework the field now operates is *preclinical Alzheimer's disease*, given operational criteria by the NIA-AA workgroup in 2011 explicitly on the premise that "the pathophysiological process of AD is thought to begin many years before the diagnosis of AD dementia" (Sperling et al., 2011). Jansen and colleagues, pooling individual data on 2,914 cognitively normal participants across 55 studies, found amyloid positivity rising from 10% at age 50 to 44% at 90, with APOE-ε4 carriers two to three times higher, and concluded that the findings "suggest a 20- to 30-year interval between first development of amyloid positivity and onset of dementia" (Jansen et al., 2015). An interval implies a trajectory. A trajectory is a disease process, not an involutional state.

That is Fischer's sentence with instruments attached.

It is worth being exact about what this does and does not settle, because the honest verdict is split rather than clean.

Fuller was right about specificity. The plaque is not diagnostic of any mental disease. Nothing has overturned that, and the modern data have made it overwhelming.

Fischer was right about signification. The plaque-positive intact brain is not merely an old brain. It is, in a substantial fraction of cases, a brain on a trajectory whose clinical end lies decades away.

Both halves are now held simultaneously, and holding both is what the field found difficult. A lesion can be non-diagnostic *and* prognostic. It can fail as a marker of present disease and succeed as a marker of future disease. Fuller had the first half and drew from it a conclusion about ageing that foreclosed the second. Fischer had the second half and bounded it inside a nosological claim — presbyophrenia specifically — that the first half would not support.

Neither man was in a position to hold both, because both were reading a cross-sectional series with a stain that showed neuritic plaques and nothing earlier. What resolves the fork is longitudinal data on living people, which neither could have.

8. What Held

8.1 Non-specificity, at scale

Tomlinson, Blessed and Roth examined the brains of non-demented old people in 1968 — the study that reopened the question in English fifty-seven years after Fuller.

Braak, Thal, Ghebremedhin and Del Tredici staged 2,332 unselected brains from ages 1 to 100 in 2011. Of these, 1,031 — 44.2% — carried β -amyloid plaques; the first appeared in the neocortex in the fifth decade in about 4% of cases, culminating in the tenth decade at 75%.

The resemblance to Fuller's 48.48% should be enjoyed but not over-read. Braak used immunohistochemistry and Campbell–Switzer silver, which detect diffuse deposits Bielschowsky misses; Fuller's population was elderly asylum deaths, heavily enriched for age and disease, while Braak's was unselected across the whole lifespan. Two large biases running in opposite directions. The agreement of the two percentages is partly arithmetic luck; the agreement of the two *age gradients* is the substantive point.

Schneider and colleagues autopsied the first 141 participants of a community cohort in 2007. Among those with dementia, only 30% had pure Alzheimer pathology and more than half carried multiple diagnoses — Fuller's §VI and Fischer's pseudopresbyophrenia. Among those without dementia, 24.2% had pure Alzheimer pathology — Fuller's §VII and Fischer's two of thirty-five. One study, both cells, ninety-six years later.

8.2 The lesion is not what correlates with the dementia

Terry and colleagues showed in 1991 that plaque and tangle counts correlate only weakly with psychometric performance while neocortical synapse density correlates powerfully. The dissociation Fuller established as a dichotomy in 33 brains is now a continuous quantitative fact.

8.3 Deposition and failed clearance — where the two men agree

This is the strongest surviving content in Fuller, and it is also the point of convergence with Prague.

Fuller: a deposit of the products of pathological metabolism, with glial and neural proliferation as "attempts at elimination" that "do not appear successful."

Fischer, in 1912: the plaque is a proteinaceous metabolic product of the brain rather than the debris of degenerating cells (Goedert, 2009).

Both are deposition theories. Both were argued against Redlich's glial-replacement reading, which was the dominant position when each man started — Fischer disposing of it by staining the glia and finding neither fibres nor proliferated cells in the lesion, Fuller by the laminar argument. And the general category was substantially vindicated when the amyloid- β peptide was identified as a proteolytic product of a membrane protein in the mid-1980s.

Fuller describes, without the vocabulary, the plaque-associated phagocyte: his glia in and about the plaques "were more frequently of the type of gliogenous phagocytic cells," and "the glia possesses scavenger functions which, perhaps, are as important as any other function of this many-sided tissue." Del Río-Hortega would not name the microglion for another eight years. Observing spider-type glia with pigment granules sending a process to a nearby vessel, Fuller writes that "the impression is imparted that in this manner a part at least of the products of pathological metabolism find their way to the blood stream for elimination" — a parenchyma-to-vasculature clearance route, in 1911.

The strongest test of whether the deposit is itself the disease was AN1792. Holmes and colleagues followed the immunised cohort to post-mortem in 2008: amyloid load was significantly lower in immunised patients than in matched controls, and seven of the eight examined, "including those with virtually complete plaque removal, had severe end stage dementia before death," with no improvement in survival or time to severe dementia. Removing the deposit did not remove the disease.

8.4 The regional and laminar detail

Frontal and hippocampal predominance, occipital sparing, white matter and basal ganglia involvement, absence of typical plaques from cerebellum and cord: broadly the modern picture, and the cerebellar observation is a real discrimination. The sulcal claim — more plaques at the lips of sulci than at the summit — is fine-grained, easy to get wrong, and correct.

9. What Did Not Hold

9.1 The ordering claim

"Well-developed Alzheimer degeneration of neurofibrils was found only in brains showing plaques." No tangles at all in seventeen non-plaque brains.

Braak's 2011 series contains 58 brains with abnormal tau "predominantly in the locus coeruleus" and no abnormal cortical tau whatsoever, and concludes that "the first plaques occurred in the neocortex after the onset of tauopathy in the brainstem." Tangles do not merely occur without plaques; on this evidence they typically precede them.

The reason is sampling. Fuller's tangle survey was cortical and hippocampal. He examined brainstem and medulla for *plaques* and found them, but his neurofibrillary observations are cortical, and the locus coeruleus — a pigmented nucleus a few millimetres across in the rostral pons — is not a structure a survey of frontal, central and hippocampal blocks will encounter. Bielschowsky silver would have shown it. He did not cut there.

This is worth stating precisely because it is a model of how a sound design produces a confidently wrong ordering: the sampling frame excluded the region where the answer lived.

There is partial exculpation in his own text. He records pre-tangle change in a plaque-free manic-depressive of 55 and reads it as an early stage of the same process. Weighted as heavily as the negative result in the seventeen, that observation would have moved him closer to the modern position.

It is also a limitation the two men share. Fischer staged a cortical, extracellular deposit; the earliest event on the tau timeline occurs in a brainstem nucleus carrying none of his lesions, decades before his stage I appears in cortex. Neither the Prague staging nor the Westborough audit is a theory of onset.

9.2 The continuum claim overreaches

Conclusion (10) is the paper's most quotable line and its most vulnerable.

Against it: fully penetrant autosomal dominant mutations in *APP*, *PSEN1* and *PSEN2* producing the full pathology in the fourth and fifth decades; trisomy 21, where a gene-dose effect produces near-universal pathology decades early; and the *APOE* allele series, which on Jansen's data shifts the age at which 15% of cognitively normal people are amyloid-positive from about 40 for $\epsilon 4\epsilon 4$

homozygotes to about 95 for $\epsilon_2\epsilon_3$. A pure intensification-of-ageing model does not accommodate an architecture that specific.

The overreach is narrower than it looks. Fuller's conclusion is restricted to *uncomplicated* senile dementia and qualified as being "on histological grounds," and conclusion (6) reserves a category — precocious senium, "something more than an early cerebral arteriosclerosis" — for exactly the cases that would prove genetically driven. What he got wrong was not the existence of a distinct early-onset entity but the assumption that it stood in a simple accelerative relation to the common late one.

9.3 What the material could not support

Case XXXIV is one brain. Fuller's §VII rests on a single positive in a group of six, five of them sampled too thinly for their negativity to weigh. He does not overstate it — he braces it with Oppenheim and Simchowicz — but the strongest cell of the design is also its thinnest, and a reader in 1911 inclined to resist had a fair statistical objection.

The reply, which Fuller could not make and the record has made for him, is that the cell has since been filled several thousand times over.

10. Why Neither Reading Took

Three separate questions get conflated here, and they have three different answers.

10.1 Alzheimer is not the actor

The name *Alzheimersche Krankheit* was not Alzheimer's doing. It was created in the eighth edition of Kraepelin's *Lehrbuch der Psychiatrie* in 1910. Goedert, reviewing the record, declines to attribute the decision to institutional politics, writing that "it is not entirely clear what compelled Kraepelin to separate this condition from senile dementia and to name it after Alzheimer," and recording the reasons Kraepelin gave: the young age of the patients, language disturbances, focal signs, severe dementia (Goedert, 2009).

Nothing in the record supports a picture of Alzheimer working to displace Fischer. Alzheimer trained Fuller and gave him the methods with which Fuller went on to argue against the Munich position; Fuller lists Alzheimer among those who see in senile dementia nothing but an intensification of normal senium — that is, on the *continuum* side of the very question at issue. Whatever the naming cost Fischer, it was a textbook editor's judgment, and the historiography treats it as such.

10.2 What happened to Fischer is not what happened to Fuller

These are different events and should not be merged.

Fischer's framework was displaced. He had chronological priority by months, a series sixteen times Alzheimer's in 1907 and 275 brains by 1910, a morphological staging of the lesion, and a clinicopathological correlation Alzheimer's single case could not make. What he lacked was a textbook. Within a decade of Kraepelin's eponym the eight-stage chronology had gone out of the literature, and the name *Sphaerotrichia* went with it. He continued to work in Prague for another three decades. He was arrested by the Gestapo in 1941 and died in the Small Fortress at Terezín in February 1942.

Fuller's paper was not displaced by a rival name. It was declined along with the other papers that said the same thing. Huebner reached the non-specificity conclusion in 1909 and was ignored. Simchowicz reached it in 1911, in a monograph of 108 brains, and was ignored. Oppenheim's plaque-rich non-psychotic man of 77 was on the record and was ignored. These were German-speaking European men publishing in the journals at the centre of the field.

That matters for a question worth asking directly: was Fuller's work buried because he was African-American? Fuller was the first African-American psychiatrist, working in a period, as his biographer puts it, "when African-American physicians were under-represented" (Mohammed, 2021), and the under-recognition of his career is a documented fact. But it will not carry the explanatory weight here, because the identical finding was declined at the centre of the field, in its own language, from authors against whom that explanation cannot be run. The neglect of the non-specificity result was disciplinary. The neglect of Fuller's name is a separate matter, real on its own terms, and conflating the two makes both harder to see.

10.3 What the naming did

A named disease with a definite histopathology is institutionally productive: it organises a clinic, a laboratory, a syllabus, a research programme. "An index of senile involution" organises nothing — it offers no entity, no boundary, and no research to do that is not simply the study of ageing. Fischer's presbyophrenia offered an entity but was bounded to a syndrome the field was already abandoning.

The position that won was not the one with the largest series, the best controls, or the most careful author. It was the one attached to the strongest institution, and it won without engaging the alternatives: Kraepelin's entry cites Fischer's monograph in passing, does not discuss the staging, and does not engage the comparison groups.

II. Assessment

Established, and reproduced at scale. Plaques occur in the brains of the non-demented aged. Dementia occurs in the aged without plaques. Plaques do not occur in the brains of the younger insane across a wide diagnostic range. Plaque burden dissociates from atrophy in both directions and is not produced by arteriosclerosis. Plaque frequency rises with age. Frontal and hippocampal predominance; sulcal-depth predilection; no typical cerebellar or cord involvement.

Established, and shared with Fischer. The plaque is a deposit around which glial and neural proliferation represents unsuccessful attempted elimination, rather than the residue of a dead neuron. Fuller's laminar argument for this remains sound as stated, and it reaches the same destination as Fischer's 1912 conclusion by a different route.

Not new, though often assumed to be. The four-cell comparison design. Fischer built it in 1907 and Fuller cites him doing so.

Genuinely added. One emphatic plaque-positive non-demented brain with hippocampal predominance and Ammon's-horn tangles; both dissociation arms tabulated in a single series; the first substantial controlled series on the question in English.

Asserted on inadequate material. That plaques are absent in most non-demented elderly brains. Five thinly-sampled formalin blocks, with a stain blind to diffuse deposits.

Refuted. That well-developed neurofibrillary degeneration occurs only in plaque-bearing brains. Refuted by brainstem sampling neither Fuller nor Fischer performed.

Overreached, and lost to Fischer. That the plaque in the intact aged brain is an index of involution rather than a presymptomatic stage. The field took Fischer's reading.

Unresolved. Whether the enrichment of plaques in senile dementia — which Fuller conceded and which is real — reflects a causal contribution, a shared upstream driver, or a marker of a process that produces the dementia by other means. That is the question the design was built to ask and could not answer.

12. Conclusion

There is a way of reading this paper that should be resisted, and it is the reading a modern audience will reach for first: that an Alzheimer-trained American pathologist, working in obscurity at a state asylum, ran the study that settled the plaque question in 1911, and that the field's failure to listen is the scandal of the discipline's founding.

It is not right. Fischer had run the controls in 1907. Fuller cites him running them. Fischer had 275 brains where Fuller had ninety-three, had staged the lesion into eight morphological types where Fuller scored presence and absence, had found that neuritic injury tracks the plaque's stage rather than its number, and had — a year after Fuller, and independently — published his own cases of dementia without plaques against his own thesis. He then spent three decades practising in Prague and died in a Gestapo prison. The morphology of the lesion, the deep clinicopathological reading, and the framework that made the plaque a staged process rather than a countable object are his, and no reassessment of Fuller displaces any of it.

What Fuller is, is the audit — and an audit is a real contribution. He tested a claim from inside the tradition that produced it, with the tradition's own stains, on material the tradition did not have. He found the answer to the narrow question and reported it plainly: the plaque is common in the demented, present in the intact, absent in the young insane, and diagnostic of nothing. He put seventeen of his thirty-three cases in the cell that undermined the lesion and gave that cell its own abstracts, its own classification analysis, and its own age table. He built a competing-disease control of fifty and declined two tempting near-misses inside it. And on mechanism he reached, independently and in English, the same deposition-and-failed-clearance reading Fischer would state in 1912 — the reading that has outlasted the one both men were arguing against.

Where he was wrong is where it is most interesting to watch him be wrong. Given a plaque-heavy brain in an intact eighty-year-old, he concluded that the man was old. Fischer, given two such brains, concluded that they were ill and had not yet shown it. A hundred and fifteen years of work has come down on Fischer's side of that, and the concept the field uses — preclinical disease, with a twenty- to thirty-year runway — is his and not Fuller's.

So the correct placement is neither hero nor footnote. Fuller is the American echo of a Prague argument: the same test, run again, four years later, in another language, on another continent, reaching the right answer about specificity and the wrong one about meaning. That is worth recovering on its own terms. It is worth recovering more, not less, if it is not sold as something it was not.

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