

# Henryk M. Wisniewski and the amyloid theory of Alzheimer's disease

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## 1. Introduction

The amyloid theory of Alzheimer's disease (AD) is now the dominant paradigm for the etiology of this particular neurodegenerative disorder, and Henryk Wisniewski played a major role in its elaboration. Together with Robert Terry, in the early 1970's, they were in a position to take advantage of the electron microscope to give a fine structural account of the appearances of A $\beta$  amyloid deposition in the AD brain. Wisniewski brought his characteristic flair to these descriptive analyses, best summarised in a review article published in 1973 §. That review has come to represent the watershed between the classic morphologic approach (commencing with Bloq and Marinesco in 1892) and the current molecular biological era. It is worth re-reading in detail, since it sets out clearly many of the paradoxes of A $\beta$  deposition that still require clarification. Let's summarize Wisniewski's analysis of the amyloid theory as it stood in 1973, and then see where his ideas have led us today.

Wisniewski started his analysis with the observation that the classic morphologic approach allowed for three types of plaques:

- a) typical plaques with a central core of amyloid surrounded by rods, granules and reactive cells;

- b) primitive plaques without a central amyloid core; and
- c) compact ("burned-out") plaques with a central core alone.

Previously, light microscopists had been unable to determine the cellular origins of the rods and granules around a typical plaque. Primitive plaques would have covered the amorphous and "cotton-wool" plaques that are currently in vogue today. The attribution of a "burned-out" nature to a plaque without neuritic or cellular reactive changes was a bold interpretative step. The relationship of intracellular neurofibrillary changes to these plaques was acknowledged to be a major question.

The advent of electron microscopy therefore permitted a precise definition of the rods and granules around a plaque, and thus suggested to Wisniewski and Terry that plaques formed in the following sequence: degeneration of neuritic terminals; attraction of reactive cells; and subsequent deposition of amyloid. To emphasise this temporal sequence, they proposed to change the terminology of "senile plaque" to "neuritic plaque", and echoed McMenemey's suggestion that "the plaque should not be accepted as a phenomenon of pure aging, but rather as a manifestation of disease". In addition to describing the fine structure of the neuritic elements and reactive cells surrounding and interweaving with the amyloid deposits, Wisniewski also drew attention to neuritic changes in the neuropil in the absence of close proximity to the larger deposits of amyloid. When numerous, however, the neuritic changes were accompanied by small bundles or wisps of extracellular amyloid. Within neurites, elements of the paired helical filaments of the neurofibrillary tangle were observed for the first time, thus linking this intracellular phenomenon to the process of neurofibrillary tangle formation in the cytoplasm and peri-somal areas of neurons.

For the morphologists of 1973, the central question "would seem to be which of the three components arrives first on the scene and is the nidus of formation?"

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Both macrophages and astrocytes may be assumed to be reactive and secondary. We are left, therefore, with either neurites or amyloid". In contrast to the amyloid theory of Divry and Schwartz (that the amyloid deposition caused neurodegeneration), Wisniewski and Terry were inclined to the alternate idea that neuritic change caused the amyloid formation: "Our inference is that aggregates of degenerating neurites induce the local deposition of amyloid, and therefore that the neurites are the nidus of plaque formation".

The 1970's marked the beginnings of the biochemical unravelling of the amyloid, beginning with studies of Nikaido and Austin, Glenner, Allsop and Landon, Bobin and Wisniewski, Selkoe, and ourselves. The purification, amino acid sequencing, and finally the cloning of the amyloid- $\beta$  protein precursor (A $\beta$ PP) has permitted the amyloid theory of AD to develop at a rapid pace. We stand today at a point where the evidence is compelling that A $\beta$  amyloid lies in the central pathway of the etiology of AD. The dominantly inherited forms of AD show clearly that mutations in the A $\beta$ PP gene or in the associated processing machinery (the presenilins) are sufficient to allow for the over-production of A $\beta$ 42 and thereby cause AD. The genetically inherited risk factors (ApoE, for example) also appear to operate through the A $\beta$  pathway. The genetically engineered transgenic mice in which A $\beta$  amyloid deposition occurs (albeit without neurofibrillary degeneration) also serve to emphasize this central amyloidogenic pathway.

How then did Wisniewski adapt his ideas and hypotheses in the light of the flood of information that emerged over the last 20 years? For a start, he continually championed the role of amyloid in AD pathogenesis, and stimulated much debate over its primary or secondary role. He never fully gave up the idea that the vascular system or reactive microglia had some major role to play. Recent discoveries on the clearance of A $\beta$  deposits from the extraparenchymal spaces of the brain following immunization with A $\beta$  itself have borne out this approach, notwithstanding the secondary role of microglia that has been demonstrated by this phenomenon. Concerning the idea that neuritic change induced amyloid deposition, it is now clear from the transgenic mouse models that the reverse situation is operative . . . but a caveat remains over the failure of these animal models to generate intracellular paired helical filaments. Wisniewski's key observations on the presence of these abnormal filamentous aggregates within the (pre-synaptic) neurites of the AD brain may yet prove to be the missing link between A $\beta$  deposition and neurite formation.

Do the three types of amyloid plaque (typical, primitive and compact) have any pathogenic significance? Their replication, to a variable extent, in the transgenic mouse models would suggest that the spectrum of plaque morphology is determined largely by the kinetics of A $\beta$  amyloid formation, deposition, and clearance. But to the extent that the type of plaque is determined by the degree of neuritic change, a salutary lesson may still be gleaned from Wisniewski's analysis. He pointed out that the Divry-Schwartz concept of the amyloid theory came "as an indivisible three-part package". This nexus between the A $\beta$  amyloid, neurites, and reactive cells needs to be kept in mind as we take the final steps towards a coherent theory of Alzheimer's neurodegeneration.

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