BASIS OF STRUCTURAL ALZHEIMER DISEASE
AND SOME PATHOGENIC CONCEPTS

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INTRODUCTION

By now it may be fairly assumed that just about everyone concerned with the
biology of this disorder is aware of its morphologic aspects. The positive
findings are the senile plaques, the neurofibrillary tangles, activated microglia
and the neuropil threads; while the negative findings are loss of neurons and of
synapses (Table 1). The plaque is comprised of a cluster of dystrophic neurites
and a few abnormal synapses surrounding a core of β-amyloid (Terry et al.,
1964). Fibrous astrocytes are prominent on the periphery, while microglia
hold a close relationship to the amyloid and are scattered in the neuropil. The
tangles are found principally within the large and medium neurons of the
hippocampal formation and entorhinal area, and in the neocortex. They are
made up of paired helical filaments (PHF) (Kidd, 1963), which in turn are
composed largely of abnormally phosphorylated tau protein (Brion et al.,
1985). Neuropil threads contain PHF and neurofilaments (Kowall and Kosik,
1987). Tangles, especially in the entorhinal and hippocampal areas, may be
left outside neurons as a result of their formative neurons having died. This is
very rare in the neocortex despite extensive loss of neurons here.

The neurons that are lost have come from populations of large and
medium sized pyramidal cells in entorhinal (Hyman et al., 1984) and
hippocampal areas (Ball, 1977), and in the neocortex (Terry et al., 1981).
Locus ceruleus (Bondareff et al., 1982), dorsal raphe (Aletrino et al., 1992)
and certain other stem nuclei may also be involved. Tangles need not be
involved in cell loss, especially from neocortex. Synaptic loss has been
measured in cortex (Scheff et al., 1990; Masliah et al., 1989) and hippocampal
(Samuel et al., 1994) areas and is significant in the neuropil between as well as
within plaques. The loss of synapses is greater than that of neurons.

Given the prominence of the two major (and oldest) findings –plaques
and tangles– it is not surprising that there are two major opposing concepts
Table I: Structural changes in AD

<table>
<thead>
<tr>
<th>POSITIVE</th>
<th>NEGATIVE</th>
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</thead>
<tbody>
<tr>
<td>• Plaques &amp; Amyloid</td>
<td>• Neuron Loss</td>
</tr>
<tr>
<td>• Tangles &amp; PHF</td>
<td>• Synapse Loss</td>
</tr>
<tr>
<td>• Neuropil Threads</td>
<td></td>
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<tr>
<td>• Activated Microglia</td>
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</table>

Concerning the primary element of the pathogenesis. These two camps have been facetiously named the "baptists," because they favor the primacy of β-amyloid protein; and the "taoists," those favoring the tangle and its tau protein. It is, however, increasingly clear that there are logical problems in both positions. Table II cites several circumstances in which β-amyloid is present without tangles and therefore, this amyloid does not necessarily induce tangles. There are other instances where tangles are present without amyloid; and so tangles do not necessarily lead to the formation of amyloid. There must be other factors involved in Alzheimer disease (AD).

Some of the argument on pathogenesis has been based on which lesion came first. Diffuse plaques, that is immunoreactive amyloid largely without formed filaments and without neurites, are found very early in Down's syndrome (Rumble et al., 1989). The assumption is often made that these diffuse plaques go on to mature as typical neuritic senile plaques. But this has not been proven, and it is not inconceivable that the diffuse plaque and the mature plaque develop as two quite separate elements with only occasional conversion. Both are present in advanced cases of the disease. The aged primate displays clusters of dystrophic neurites without amyloid prior to the presence of fully formed typical plaques (rarely with PHF in the neurites) (Wisniewski et al., 1973). In electron microscopic studies of human brain biopsies, it was noted that the subtlest lesion was made up exclusively of dystrophic neurites without amyloid, and that amyloid appeared only when there were three or more such neurites clustered together (Terry and Wisniewski, 1970). The Athena mouse displays synapse loss preceding the appearance of amyloid (Masliah, 1996). Thus, amyloid may well not be the leading event.

Table II: Does the one cause the other?

<table>
<thead>
<tr>
<th>PHF without significant amyloid</th>
<th>β-amyloid without PHF</th>
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</thead>
<tbody>
<tr>
<td>Post-Encephalitic Parkinson's disease</td>
<td>Normal Aging</td>
</tr>
<tr>
<td>Guam Parkinson – Dementia</td>
<td>Plaque-only dementia</td>
</tr>
<tr>
<td>Tuberous Sclerosis</td>
<td>Ischemia</td>
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<tr>
<td>Subacute Sclerosing Pan Encephalitis</td>
<td>Lewy Body Variant</td>
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<tr>
<td>Dementia Pugilistica</td>
<td>Arterio-Venous Malformation</td>
</tr>
<tr>
<td>Niemann-Pick type C</td>
<td>Athena tg Mouse</td>
</tr>
<tr>
<td></td>
<td>Aged Primate</td>
</tr>
</tbody>
</table>

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