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Pathobiology of Alzheimer's disease: A morphologist's view

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Perhaps no other disease of the human brain has aroused more interest than Alzheimer's disease. The subject continues to be a fertile field for modern neurobiology. The classical morphologic hallmarks include: regional neuronal loss, neurofibrillary tangles (NFT) in neurons and senile plaques (SP) (neuritic plaques) in the neuropil, particularly in limbic and associated cortices. Similar and qualitatively indistinguishable changes occur, though in much smaller numbers, during normal ageing. However, only limited correlation of these lesions with cognitive dysfunction has been reported. NFT consist of highly insoluble paired helical filaments, considered characteristic of Alzheimer's disease, and antigenically related straight filaments. These also accumulate within neurites in and around SP. They are derived from cytoskeletal proteins, particularly microtubule associated protein, tau. In contrast, extracellular amyloid filaments, found in the centre of many of the plaques and in meningeal and cortical vessels, appear to be composed of a hydrophobic, low-molecular weight polypeptide, the β-amyloid protein. It has a novel amino-acid sequence, including a domain thought to be in close association with the plasma cell membrane. Like other amyloids, it is derived from a larger precursor protein and self assembles to form large aggregates. Segments of the β-amyloid protein, when studied in vitro, have been found to be neurotoxic to mature neurons and neurotrophic to immature ones. Exactly how these aberrant polypeptides in and around the neurons lead to dementia is still a matter of intense investigation. Recent studies have emphasized synaptic loss as a major correlate of cognitive decline. It will, therefore, be important to investigate the role of β-amyloid in that process.

To explain the evolution and progression of the lesions, a causative role for environmental trace metals has been invoked, but such a role remains unproven. Since it is alleged by some that Alzheimer's disease is not prevalent in India, cross-cultural epidemiologic studies would be of importance. Its age-specific prevalence and incidence in India, however, remains unknown.

ALZHEIMER'S disease (AD) is one of the commonest causes of dementia, a symptom complex characterized by acquired global impairment of intellect, memory and

personality, without impairment of consciousness. During the evolution, at milder levels of expression, it is difficult to distinguish AD from cognitive deficits observed during natural ageing[1,2]. Even at the pathomorphological level, some of the cellular changes noted in AD are also observed in ageing, thus raising the question – is this disease an exaggeration or acceleration of the natural process of senescence? During the last decade an intense focus on this disease has resulted in a plethora of structural, biochemical and molecular biological observations, defining new features in a disease first characterized 80 years ago[3]. The central objective of this biological research on AD is to understand the molecular changes that cause premature dysfunction and death of neurons in selected anatomical areas of the brain. At present there are no laboratory studies specific for the clinical diagnosis of AD. The diagnosis is essentially one of exclusion and a definitive diagnosis can only be made by examination of the brain tissue by biopsy or at autopsy[2]. In the near future, new imaging techniques like MRI, PET, etc. which permit evaluation of regional changes in the brain structure, function and transmitter-specific circuits may provide new insights into the relationship between the clinical neuropsychological symptoms and brain abnormalities.

Based on the age of onset and clinical progression, AD is conventionally divided into presenile and senile dementia. Another disease, Down's syndrome, which starts in early life, also reveals pathomorphological features in the brain of adult Down's syndrome patients identical to AD. It appears that all the three clinical expressions, AD, senile dementia of Alzheimer type and Down's syndrome, represent a disease with a final common pathway, but with variable temporal evolution and molecular genetic variables. The following paragraphs will be largely concerned with morphology and include some comments on the pathogenesis of the AD-associated lesions.

Gross brain changes. Macroscopically, the traditional feature associated with AD is shrinkage and atrophy of the brain, involving the frontal and temporal lobes preferentially[4]. In AD (senile type) beyond the age of 65–70 years, the cerebral atrophy may not be marked and may be quantitatively overshadowed by the decrease in the brain size due to the natural ageing process. However, it is generally thought that severe cerebral atrophy is more common in presenile (less than 65 years of age) than in the senile group. The thickness of the cortical mantle in the cerebral gyri is reduced[5] by 15%, a feature not easily appreciated with the naked eye. Loss of hemispheric white matter has been noted, which may equal or exceed that of the grey matter[6]. This partly explains the ventricular dilation observed radiologically and on gross examination. Coexistence of

ischaemic lesions and traumatic lesions in AD is no greater than in age-matched controls, an important observation suggesting that neither vascular pathology nor past head injury contribute to the development of the disease[7]. However, AD can coexist with substantial ischaemic lesions in the brain, justifying the additional diagnosis of multi-infarct dementia (MID).

Microscopic changes. In Alzheimer's disease, the affected neurons reveal several types of cytoskeletal pathology. Essentially a triad of histological features form the hallmark of AD, viz. neurofibrillary tangles (NFT), senile plaques (SP) and granulovacuolar degeneration (GVD). Though associated nerve cell loss in various regions of the brain is an invariant feature, it does not lend itself for easy evaluation to aid the pathological diagnosis.

The NFT are intracellular, aberrant aggregates of the native neurofilaments in neurons located in hippocampus, neocortex, basal nucleus of Meynert and some brain stem nuclei like locus ceruleus and raphe[8,9]. These NFT are large, non-membrane bound, flame-shaped or globose masses of abnormal filamentous aggregates curving through the perinuclear cytoplasm and often extending into the apical dendrites (Figure 1). These are easily demonstrable by various silver stains. Widespread NFT are found in fully evolved AD, both sporadic and familial, and in cases of Down's syndrome after 40 years of age. Surprisingly, in some cases of senile dementia of Alzheimer's type, very few NFT may be found in the neocortex[10]. In such instances and in nondemented elderly individuals, NFT are usually confined to the restricted domain of hippocampus (CA_1 area) and entorhinal cortex[11]. Extracellular residue of the NFT found in abundance in hippocampus and neocortex represent the 'tomb stones' marking the sites of 'once alive' neurons. The mechanism of their degradation and removal (scavenging) is not clear.

The NFT are highly insoluble. Ultrastructurally, they are made up of paired helical filaments (PHF) (Figure 2) approximately 10 nm wide and wound around each other with a cross over every 80 nm[12,13] and or 10 20 nm straight filaments[14]. Immunochemically, NFT react with antibodies to phosphorylated neurofilaments, microtubule-associated proteins (MAP-2), 'tau' and ubiquitin[15–19]. These filaments reveal a high degree of phosphorylation[20], thus probably imparting rigidity and insolubility. 'Tau' is the major component of PHF, the characteristic component of NFT found most abundantly in AD brains[21]. Another constituent protein of PHF, viz. A 68 is considered to be derived by post-translational modification of highly phosphorylated 'tau' in neuronal perikarya[22–24]. As this protein (A 68) is found only in AD brains, and not in normal ageing cortex, it has enjoyed the status of a 'marker protein' for the diagnosis of Alzheimer's disease, detected by a
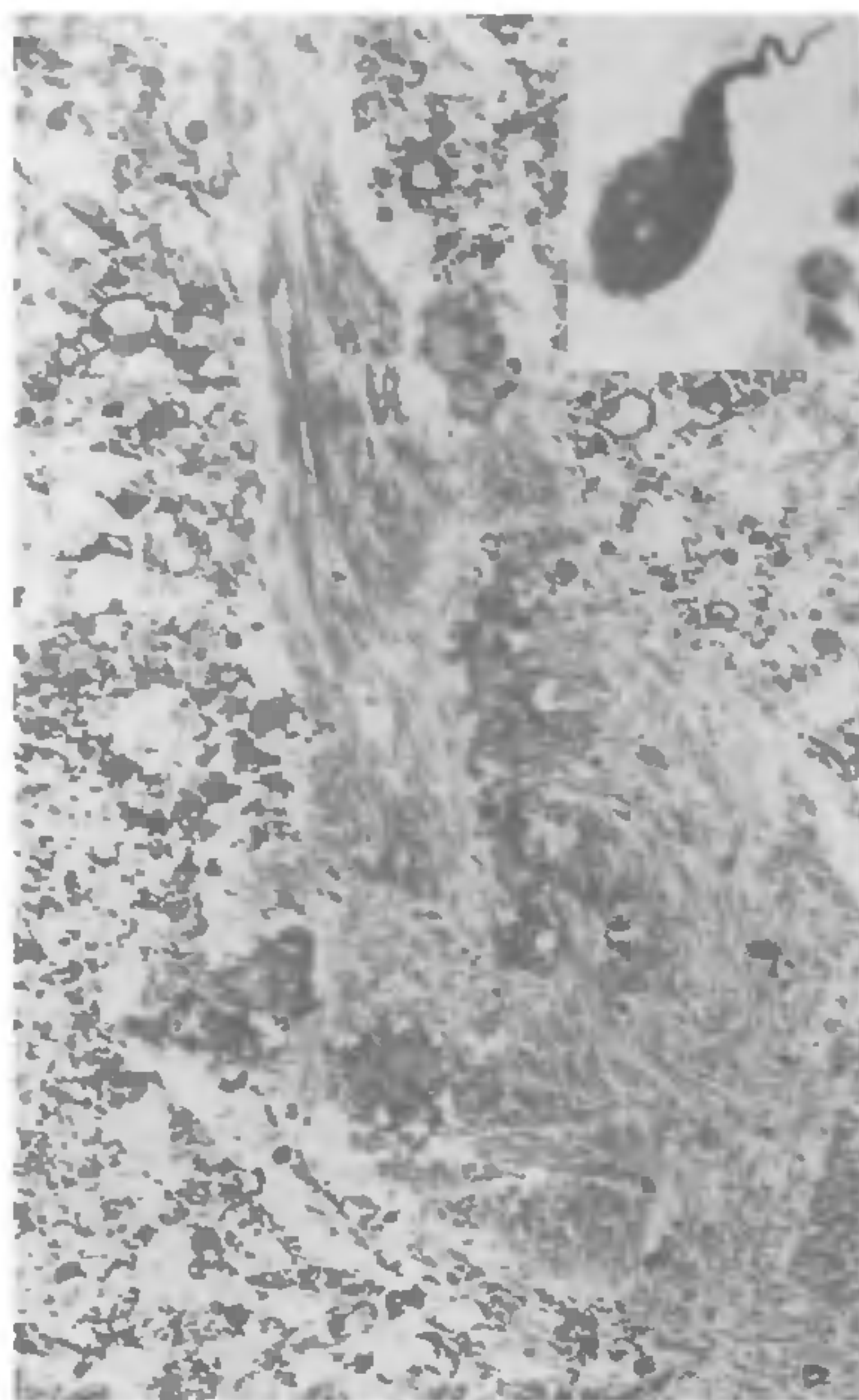
Figure 1. Low power electron microphotograph showing neurofilamentous material almost filling a neuronal cell body. A few masses of lipofuscin are seen in the central portion. (×3500) *Inset*: A neurofibrillary tangle (NFT) in a neuron from the frontal cortex Von Braunmuhl silver stain (×480) Senile dementia of Alzheimer type in 73 year-old male from Bangalore
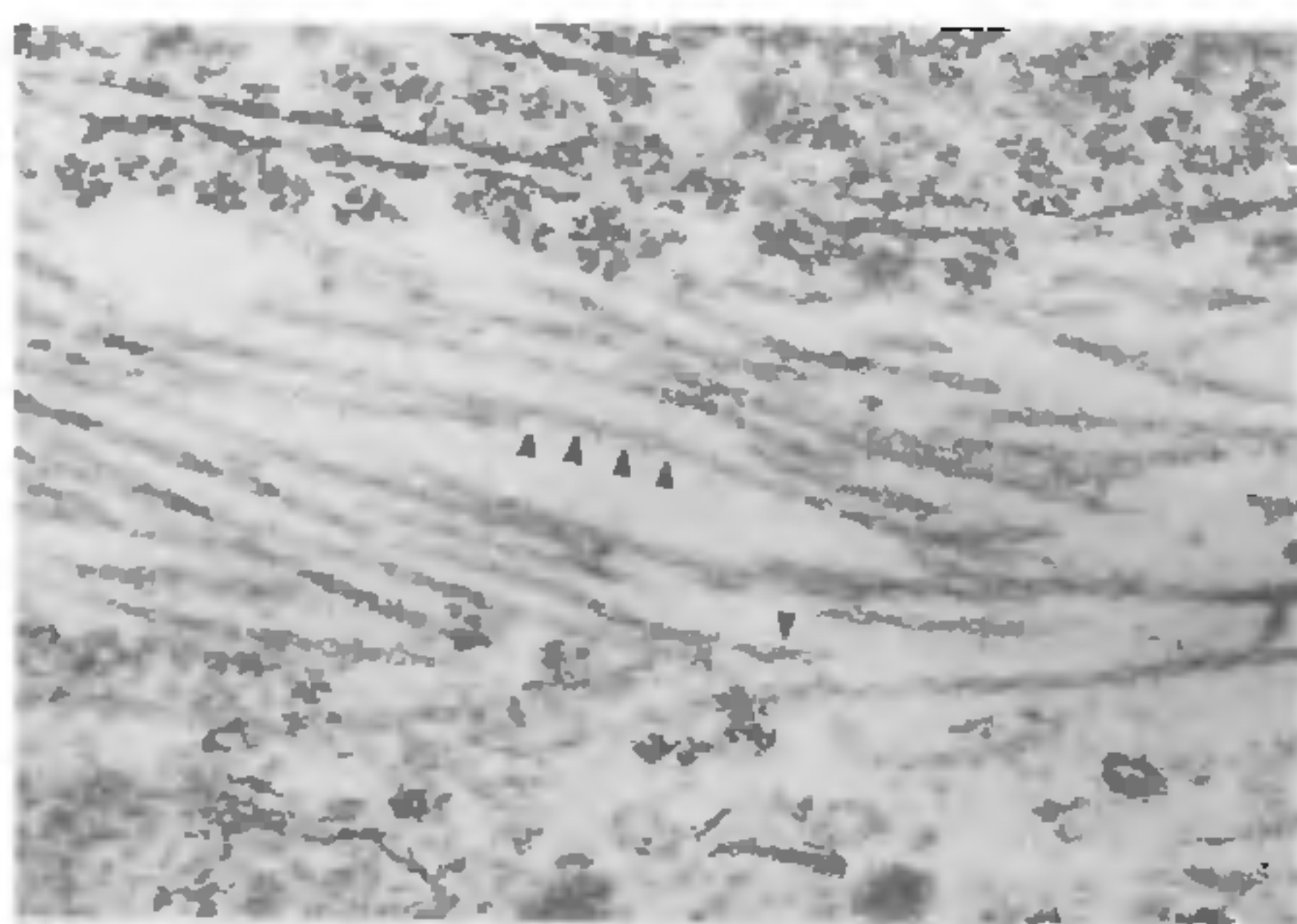
Figure 2. Electron micrograph demonstrating paired helical filaments (PHF) in a neuronal cytoplasm. The arrow heads point to 80 nm periodic constrictions in the PHF. Note rough endoplasmic reticulum in the top portion of the figure. Lead citrate-uranyl acetate. (×60,000). Same as in Figure 1.

monoclonal antibody, Alz 50. The degree of dementia in AD has been found to correlate with the number of NFT and accumulation of PHF in various anatomical areas of the brain[25-27]. This suggests that this cytoskeletal pathology may be associated with changes in the dynamic properties of neurons, whose formation and elimination are important in the clinical expression of the disease. In experimental studies[28], electrical activity could be recorded in the cerebral cortical neurons of cats unaffected by NFT, but the neurons with NFT induced by aluminium had selective failure in electrical activity in post-synaptic membranes, suggesting a viable state of these cells but an aberrant electrical physiology. Though similar data are lacking in the human system, the same may be true. It is important to realize that experimentally induced NFT in the animals by the application of aluminium salts differ antigenically and ultrastructurally, though they look similar to human NFT of AD through routine silver staining[29].

Another morphological feature noted in AD brains is the presence of 'neuropil threads' and 'dystrophic neurites' in the cerebral cortex. Similar to NFT these are noted to a limited extent in the brains of the elderly. They are thread-like, short, slender, distorted structures, seen extracellularly, between the neurons. Electron microscopic studies have revealed these neuropil threads to be related to dendrites of the NFT-bearing neurons[30]. Similarity in the antigenic character of these structures to NFT further indicates that they arise from the same alteration of the cytoskeleton in the neuronal processes. The neuropil threads are like the NFT in AD and are in contrast to those noted in brains of the normal elderly, in that they immunoreact with antibodies to 'tau' and the 'tau'-related A 68 antigen[23,31,32]. The neuropil threads and NFT appear to form during the evolution of AD, but do not necessarily contribute to the formation of the senile (neuritic) plaque[33], another extracellular pathomorphological lesion in AD.

Neurons of the olfactory epithelium, which are of central origin and which undergo constant turnover because of their 'neuronal stem cell nature', also show some of the structural and immunochemical pathology characteristic of AD. The neurons and nerve bundles stain with Alz 50 and Tau antibodies, as in NFT[34,35]. Clinical defects in odour detection and discrimination are observed in AD. This area, because of its anatomical location, is accessible for easy biopsy and evaluation.

The second and important hallmark of AD is the 'senile plaque' (SP) also known as the 'neuritic plaque'. These are spherical, complex, extracellular structures of 100–150 μm diameter, made up of both neuronal and non-neuronal elements (Figure 3a). They are composed of aggregates of abnormal nerve terminals and dendritic

processes admixed with astrocytic and microglial elements and extracellular beta amyloid protein. Like all amyloids, this material is highly insoluble, stains with the congo red dye (exhibiting a dichroic birefringence under polarized light) and with the electron microscope, consists of polypeptide fibrils 6–10 nm in diameter presumably corresponding to a beta-pleated sheet configuration of the aggregated amyloid polypeptides. The neurites are the enlarged and dystrophic axonal terminals filled with filaments,
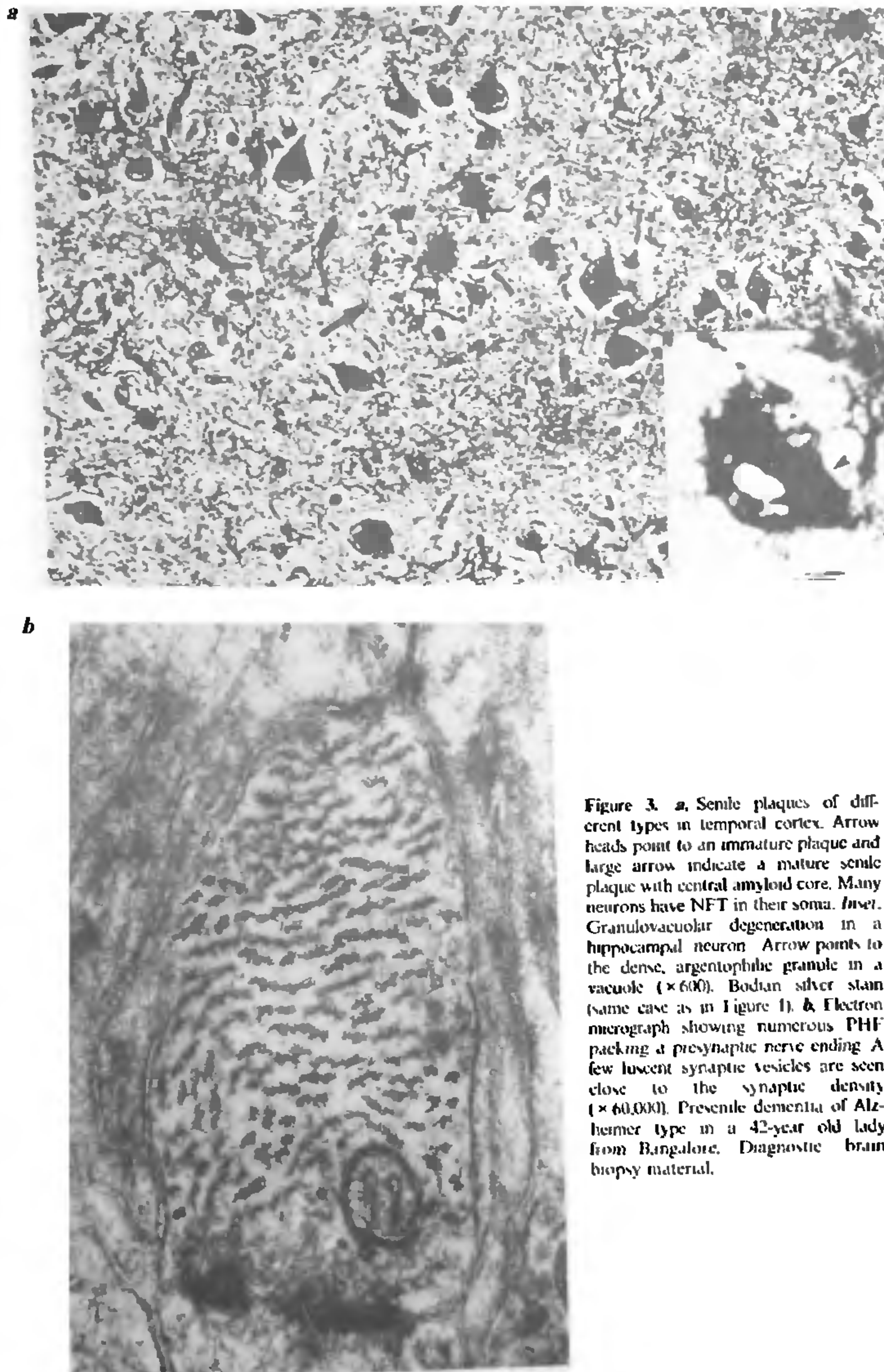
Figure 3. *a*, Senile plaques of different types in temporal cortex. Arrow heads point to an immature plaque and large arrow indicate a mature senile plaque with central amyloid core. Many neurons have NFT in their soma. *Inset*, Granulovacuolar degeneration in a hippocampal neuron. Arrow points to the dense, argentophilc granule in a vacuole (×600). Bodian silver stain (same case as in Figure 1). *b*, Electron micrograph showing numerous PHF packing a presynaptic nerve ending. A few lucent synaptic vesicles are seen close to the synaptic density (×60,000). Presenile dementia of Alzheimer type in a 42-year old lady from Bangalore. Diagnostic brain biopsy material.

including PHF (Figure 3b) and membrane-bound dark bodies of mitochondrial and lysosomal origin[36,37]. The majority of these structures represent degenerating neuronal elements, while others suggest abortive regenerates. The SP are a common feature in the brains of the normal elderly. They occur in over 80% of humans reaching tenth decade[36] and are also encountered in the brains of aged mammalian species of animals like dogs, monkeys, and polar bears[38]. In AD, they occur both in the neocortex and archicortex (phylogenetically old), while in normal ageing they are concentrated in the archicortex. Based on the morphological features and suggested temporal evolution, essentially three types of plaques are distinguished: (a) The primitive plaque or atypical plaque, composed of scattered wisps of amyloid fibrils interspersed between swollen neurites; (b) The classical or mature plaque with central compact masses of amyloid surrounded by a corona of swollen neurites and processes of glial elements; (c) The compact or 'burn-out' plaque, consisting of a star-shaped amyloid core with a surrounding glial scar. These plaques disrupt the neuropil and displace the neurons. Recent studies indicate that cholinergic, and monoaminergic neuronal systems participate in the formation of the senile plaques[39]. Immunochemically, the dystrophic neurites show reactions similar to NFT and neuronal threads with various antibodies[31,32,40]. A positive correlation between the degree of cognitive dysfunction and the numbers and distributions of SP in the cortex and cognitive dysfunction has been suggested[25,27]. However, Tomlinson et al.[25,26], following the evaluation of a large number of autopsied brains, noted that in the brains of some demented subjects, very few NFT and SP could be observed.

Recently, another variant of SP, a 'preplaque' or diffuse, amorphous plaque has been recognized[41]. Ultrastructural studies have confirmed the absence of amyloid fibrils, while immunohistochemistry has revealed the presence of polypeptide segments of amyloid-associated protein[42,43]. Interestingly, a large number of these diffuse plaques have been recognized in the hypothalamus and cerebellum of AD cases, in contrast to other types of plaques noted in the neocortex and hippocampus[44]. Unlike those in the cortex, hypothalamic and cerebellar plaques do not contain immunoreactive epitopes of amyloid precursor protein (APP), tau, NF or MAPs, but do contain ubiquitin-reactive regions[44].

Some AD patients have deposits of amyloid along the walls of the leptomeningeal and intracortical vessels. The chemical nature of the vascular amyloid and the plaque core amyloid was found to be essentially similar[45,46]. Based on this observation, it has been suggested that the amyloidogenic serum protein reaches the neuropil via a damaged blood brain barrier subsequently forming the plaque core amyloid. In some plaques, by serial sections and high voltage

electron microscopy, an association of vascular elements with the amyloid core has been shown[47]. Typical plaques as well as preplaques are often found around intracortical congophilic vessels, lending further support to the hypothesis of a vascular origin of beta amyloid. Amyloid in the walls of the cerebral vessels may be found in conspicuous amounts in almost all cases of AD, in some aged individuals and in Down's syndrome. Two separate surveys of a large number of brains of clinically and pathologically diagnozed cases of AD revealed that more than 90% of these cases had associated cerebrovascular amyloidosis, whereas no case had cerebrovascular amyloidosis unassociated with senile plaques and NFT. Age-matched controls, including those with hypertension, in which SP and NFT were uniformly absent, failed to show cerebrovascular amyloidosis[48]. This shows the close association of the triad of pathological lesions in AD. In addition, it also indicates a probable mechanism of evolution of the lesions from a common protein precursor.

In granulovacuolar degeneration – as the name aptly describes – the neurons show 3–5 nm vacuoles with a limiting membrane containing a single densely baso-philic, argyrophilic particle of 0.5–1.5 nm diameter (Figure 3a). They occur singly or in multiples, exclusively in the pyramidal neurons of hippocampus, but not in the neocortex. Immunochemical studies have revealed that these granules show immunoreactivities against tubulin[49], ubiquitin[40] and phosphorylated high-molecular weight NF[50,51]. Recently, Bondareff et al.[52] have shown sequestration of tau molecules related to PHF in GVD, with a difference in the way the repeat regions of 'tau' are incorporated. The occurrence of GVD in hippocampal neurons, also vulnerable to NFT formation in AD, suggests an alternate pathway of dealing with the aberrant molecular complex by the neurons. Similar to NFT, the presence of GVD in the pyramidal neurons of the hippocampus correlates with the degree of dementia, suggesting a probable role of this cytoskeletal pathology in affecting the neuronal function.

Hirano bodies (rod-shaped, oval, eosinophilic inclusions in neuronal soma or dendrites) are commonly seen in the pyramidal cell layer of the hippocampus of AD patients. Electron-microscopically, these structures are found to have a paracrystalline form[53] and show 'actin-like' immunoreactivity[54]. Hirano bodies, unlike other cytoskeletal derived masses, are not specific for any disease and are seen even in normal states.

Synaptic pathology in AD. Ultrastructural studies of the senile plaques have revealed participation of presynaptic terminals as one of the structural components[55,56]. Quantitative electron microscopic studies on brain tissue from cases of AD have shown 25–40% synaptic loss in various zones of the brain[57]. Topographically,

the synaptic depletion was found more in hippocampus, entorhinal cortex, frontal and occipital cortex, and in the nucleus basalis and locus cereleus, the subcortical areas. This further supported the idea that AD is characterized by extensive presynaptic terminal loss, essentially in the neocortex. Immunochemical[58] and immune electron microscopic[59] studies of brain tissue using antibodies to synaptophysin revealed that the degree of synaptic loss and pathology was greater than the degree of neuronal loss. Moreover, the synaptic pathology appeared to precede the deposition of amyloid fibrils in the plaques. These findings may be interpreted to imply that, in AD, the synaptic pathology, is primary and not merely a secondary reflection of the neuronal damage and loss. It is to be kept in mind however that there are as yet no systematic comparative data on the patterns of synaptophysin immunoreactivity and synaptic alteration in various 'at risk' areas of the brain in the normal aged. Such studies will be required in order to make further meaningful inferences.

Structural alterations are noted in a variety of neurotransmitter circuits in cases of AD, including cholinergic, peptidergic and monoaminergic systems[39,60,61]. Neurons within the basal fore brain provide the major cholinergic innervation of the cortex. In AD, dysfunction and death of these neurons appear to be responsible for reduction in cholinergic markers, viz. activities of choline acetyl transferase, acetylcholine esterase, uptake of ^{3}H-choline and synthesis of ace.ylcholine from labelled glucose. Many patients with AD show changes in monoaminergic neurons, including noradrenergic and serotonergic nerve cells of locus cereleus and raphe, respectively. Somatostatin-containing neurons show NFT and the levels of somatostatin receptor in the cortex are reduced. Corticotrophin-releasing factor (CRF) immunoreactivity is also reduced in the cortex, with reciprocal upregulation of CRF receptors. Degenerative changes also occur in the nerve cells of amygdala and hippocampus and associated circuits. However, the transmitter specificities of these vulnerable neurons have not been clarified. Some of these neurons are thought to use excitatory amino acids as neurotransmitters.

A perusal of the literature on the regional and cellular pathology and neurochemical studies in different types of dementia brings out some commonalities in the cell groups or topographic regions of the brain at risk and the associated neurochemical defects[7,62]. The cholinergic defect, the cytoskeletal (both structural and immunochemical) aberrations with or without associated amyloid-related protein deposition, considered to be responsible for the cognitive impairment in AD, are observed in a host of other neurodegenerative diseases. These include Parkinson's disease (especially with dementia)[63], the Parkinson's-dementia complex

of Guam, Down's syndrome, Gerstmann–Straussler syndrome, progressive supra-nuclear palsy and dementia in boxers[64]. The suggested cause-and-effect relationship of the pathological lesions in dementia thus becomes somewhat problematic, especially considering the example of patients with Parkinson's disease, who, in spite of more than 70% cholinergic degeneration, show only mild cognitive defects[63]. Similarly, in Guam, many young adults with no neurological or cognitive deficits show significant cytoskeletal pathology in the hippocampus, an important anatomical area associated with memory[65,66]. This suggests that, in addition to the much stressed cholinergic defect and pathological changes, some other factors participate and modulate the expression of the dementing process.

A few cases of AD have been reported to show mild to moderate degrees of cortical vacuolation[67,68]. Furthermore, the brain material from two cases of familial AD, when injected into primates, induced lethal, progressive, spongiform encephalopathy although this could not be subsequently replicated[69]. This infrequent pathological feature in AD is found to resemble to a certain extent that noted in a transmissible prion disease and Creutzfeldt–Jakob disease (CJD). Curiously, CJD and related disorders like Kuru and Gerstmann–Straussler disease in humans, and scrapie in sheep, reveal substantial numbers of plaques with amyloid in the brains and are clinically present with dementia in humans, thus sharing features with AD[70]. This has raised the possibility of an infectious aetiology of AD. Molecular genetic studies, however, have shown that these are two distinct classes of disease that merely share some morphological and clinical parameters[71]. Coincident occurrences of AD and CJD pathology in the same patient have been recorded[70,72,73].

Co-localization of calcium, aluminium and silicon in the plaque core[74,75], the former two in NFT[76,77], and the association of Guamaniam Parkinsonism–dementia complex in Pacific Islands with low dietary calcium and magnesium and high aluminium[78] has raised the tantalizing question of a possible role of similar environmental factors in the evolution of AD-related lesions in the brain. Interestingly, the aluminium encephalopathy that was sometimes observed following dialysis does not result in similar neuropathological lesions.

In vitro, NF are noted to bind calcium and aluminium with great affinity, apparently related to the degree of NF phosphorylation[79,80]. The co-localization (sequestration) of calcium and aluminium could well be more the result of earlier cytoskeletal pathology in the neurons, with the participation of highly phosphorylated NF and 'tau', than of initiator/pathogenetic influence in Alzheimer's disease. The same may be true for the case of the Parkinson dementia complex of Guam. The buffering of calcium by NF may in fact keep the

calcium-activated proteases from damaging the pre-synaptic terminals, thus reducing neuronal damage, which is central to Alzheimer's disease.

Since NFT are observed in diverse neurological diseases, they are not specific for AD. This is also true for the case of tau and ubiquitin, integral components of the cytoskeletal pathology. The PHF formation could be a final common pathway leading to neuronal dysfunction and slow degeneration. The beta amyloid protein, on the other hand, may be considered to be characteristic of AD. The hope that knowledge of the protein chemistry and molecular genetic changes that precede the amyloid deposition and neuronal degradation in AD will provide clues to reverse the devastating disease and also shed light on the mechanism of normal ageing, has brought together the neuropathologist and the molecular biologist, with dramatic results. This has led to the identification of a 4-kDa protein, referred to as beta amyloid, βA_4, or Aβ. This polypeptide is derived by proteolysis of the larger amyloid precursor protein and deposits in vascular walls or in senile plaque cores in the brains of individuals with AD or Down's syndrome or normal aged subjects[81,82]. However it appears that the degree of dementia, the cardinal feature of AD, is linked to the quantum of NFT, SP and neuronal loss rather than the concentration of amyloid in the brain.

Recent molecular biological studies have helped to identify the gene encoding the beta amyloid precursor protein (β PP) and to localize it to the long arm of chromosome 21 (ref. 83). The gene regulating β PP is expressed in various normal human and animal tissues and is highly conserved in evolution. It is suggested that an aberrant proteolytic processing of the precursor may result from an inhibition or lack of inhibition of a protease and subsequent conformational change/poly-merization to a β-pleated, rigid, insoluble sheet of amyloid in the neurons and other tissues[84]. Though this protein has been well characterized biochemically, its primary biological function and role in pathogenesis of AD are not known. As with the cholinergic defect and the dementia, a long list of diseases having amyloid-related proteins in brain lesions includes all of those mentioned earlier (except hereditary olivopontine cere-bellar degeneration and Korsakoff's psychosis). This suggests that the amyloid protein may also be a nonspecific modulator influencing the neuronal mem-brane function in specific target areas in the brain, leading to cell degeneration and slow death. Many younger patients of Down's syndrome dying between the ages of 15 and 25 years show focal deposits of Aβ or β PP in the diffuse plaques, in the absence of neuritic reaction and NFT formation[85]. These plaques may be present as harbingers 10–20 years prior to the development of full-fledged AD, thus indicating the slowness of the temporal evolution. Thus, a possibility must be entertained that the nondemented individuals

having both tangles and plaques at autopsy may represent preclinical cases of AD.

Clues to the function of β PP in neurochemical physiology must lie in the structural features of the various extracellular domains of this cell membrane-associated protein. Yanker et al.[86] suggested that, in vitro, a 25–35 amino acid fragment of Aβ is neurotropic to embryonal hippocampal neurons at low concentration and neurotoxic to mature neurons at higher concentration. The identity of a processed form of one isoform of β PP with protease nexin-II suggests a role in growth regulation of neurites[87,88]. The high concentration of APP in granules of platelets would suggest a function for β PP in the coagulation cascade, wound healing and tissue repair process[89-91]. This association is further supported by enhanced immuno-localization of tissue factor antigen (tissue thrombo-plastin) in the senile plaques of AD[92]. The close asso-ciations with amyloid deposits of complement factors, acute phase proteins like α'-antichymotrypsin[88,93], serum amyloid P[94], ubiquitin and activated microglia[95] sugg-est that a slow inflammatory process is in progress in senile plaques. A differential response of neurons to vari-ous fragments of β PP[96] and variation in the gene expression and synthesis of β PP under the influence of viruses, infections, toxins, trace metals and other unknown environmental factors could modulate the dementing process.

With this vast amount of knowledge, there still remains the question—is AD an aberrent acceleration of normal ageing or a separate and distinct entity? It is generally accepted that tangles, plaques and other morphological changes in AD brain, such as amyloid angiopathy and granulovacuolar degeneration of pyra-midal neurons, are qualitatively indistinguishable from the lesions accompanying normal ageing of human brain, but are quantitatively much increased in AD. However no definitive answer yet has been provided to the question—are these structural changes responsible for dementia?[97]. If they were to be the cause, occurring at a greater pace in AD, a stage should be reached in human ageing where most individuals should end demented and bear quantitatively similar neuronal lesions in the brain, comparable to AD. If the quanta of the cytoskeletal pathology in neurons is the crucial factor for dementia, it does not explain the genesis of cognitive derangement noted in cases clinically diagnosed as AD, but with much less pathological lesions in senile dementia of Alzheimer's type and other forms of dementing illness without these pathological stigmata[98]. On the other hand, amyloid accumulation is a well-recognized hallmark of pathology in AD and a fair amount of accumulation occurs in normal ageing. At the cellular level, increased gene expression of the beta-amyloid precursor protein in senescent cultured fibro-blasts indicates a direct relationship between normal bio-

logical ageing and amyloid deposition[99]. It is plausible to suggest that an ill-regulated expression of amyloid or its variable fragments and its noxious influence on topographically specific and 'at risk' neuronal populations lead to the dementing illness of Alzheimer's type. Another apparently unrelated observation probably provides a clue to the puzzle. The monoclonal antibody Alz 50, which specifically recognizes a 68-kDa protein (A68) present in the brain of AD and older Down's syndrome patients, but not in the normal aged, has been found to react with normal foetal and neonatal neurons. This suggests an aberrant reactivation of a developmentally regulated growth mechanism in AD[100,101].

The hypothalamus, the prime anatomical site in the brain involved in controlling stress-related responses and neuroimmunomodulation, shows less of the neuropathological hallmarks of AD, even in full-blown cases. It will be of great interest to study structural, neurochemical and immunomodulatory aspects of this anatomical site in various neurodegenerative diseases. This may hold the key to unravelling the mystery of Alzheimer's disease. If beta amyloid precursor proteins or small fragments of these are proved to be neurotoxic and the initiating factor for neurodegeneration, a search has to be made for substances which, by a specific receptor-mediated action, can reverse this relentlessly progressive degenerative process.

It is generally felt that in India, AD is rare. Based on a limited study of autopsied brains of aged individuals from one centre in South India, an apparent paucity of NFT and senile plaques in aged Indian brain, compared to the West, has been reported. However, no meaningful epidemiological data on dementia, especially senile dementia of Alzheimer's type, are available from India, and such is also the case in most of the developing countries[102]. So far only two psychometrically evaluated and pathologically, ultrastructurally and immunologically characterized cases of AD have been recorded in India, and these were in no way different from the ones reported from the West[103]. Given the age structure of the Indian population, the number of dementia patients may not be as large as in the developed countries. With longer life expectancy in the next decade, however, India may have more cases of dementia of the Alzheimer type. As indicated in Figure 4, if infections were to be the major modulating and promoting factors for increased synthesis of cerebral amyloid, it is logical to expect higher frequencies of NFT and SP in the brains of the aged from India. With high prevalences of leprosy and tuberculosis and other chronic infections, systemic amyloidosis is not infrequent in our country. Brains of patients with subacute sclerosing parencephalitis (SSPE), a post-measles, slowly progressive viral encephalitis, is known to have NFT, similar to those of AD. Due to an

Amyloid Protein and Dementia

(Probable role/mechanism)

Amyloid precursor protein — 695 amino acids
(principal isoform in neurons)

39–42 amino acid fragments (4 kDa)
constitute beta amyloid in NFT plaque cores and in amyloid angiopathy

In human brain APP_{695} mRNA highest in

Frontal cortex (layers III and V)
Hippocampus
Visual cortex (Tanzi et al.[104])

(Purkinje cells of cerebellum, oligodendroglia, fasicular astrocytes, vascular endothelial cells, meningeal cells also express)

Alzheimer's disease : APP_{695} mRNA expression ↑ ↑ ↑
(Higgins et al.[105])

APP mRNA expression ↑↑↑ — by interleukin-I
Heparin binding growth factor-I
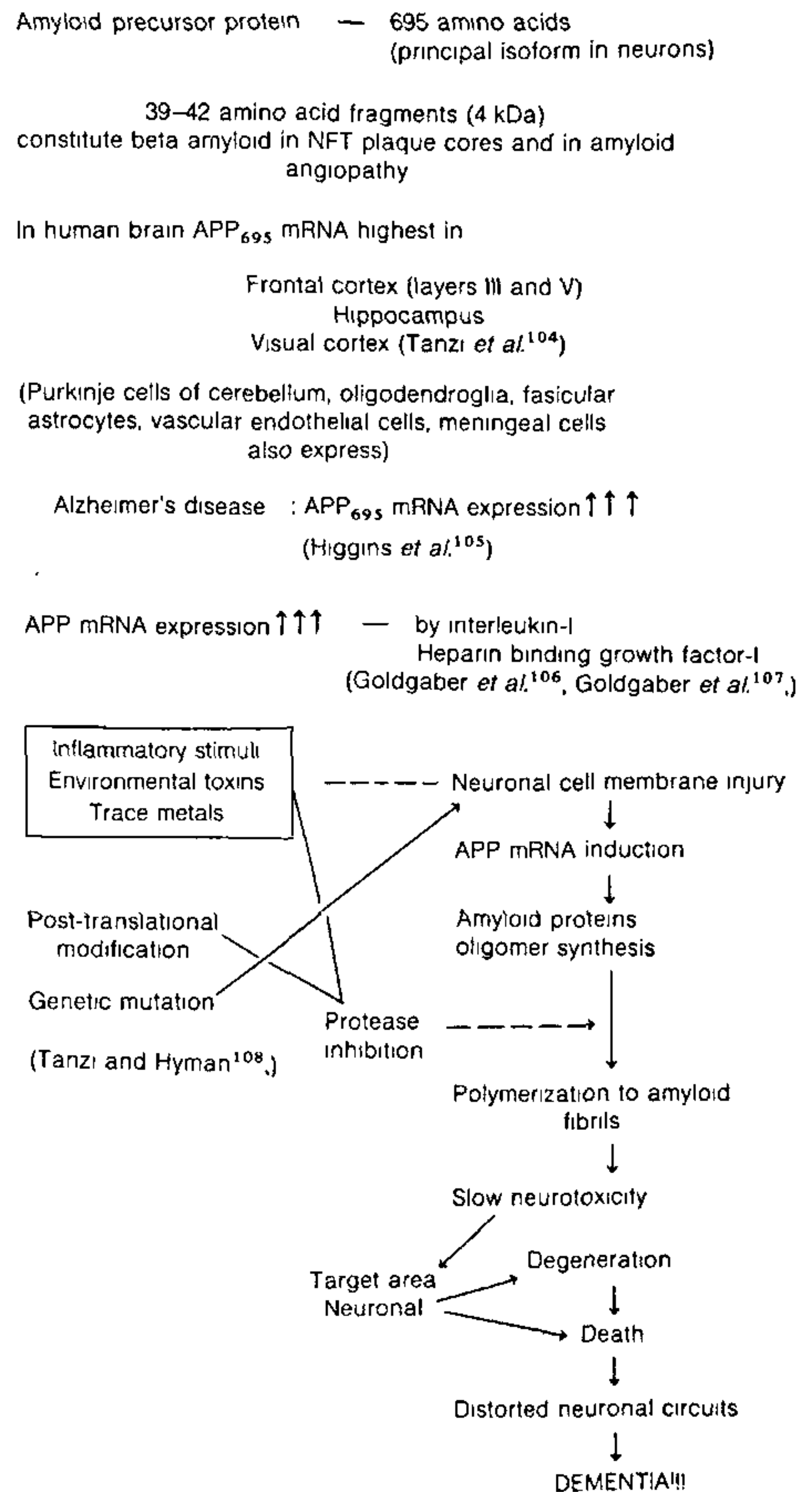(Goldgaber et al.[106], Goldgaber et al.[107].)

Figure 4.

ineffective vaccination programme, measles and SSPE are frequently encountered in India. If AD-related neurological and psychiatric illness is really infrequent, an in-depth investigation is needed to look for factors which protect 'Indian brains' from accumulating beta amyloid and thereby reducing the risk of AD.

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