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## Alzheimer disease models and human ~~neuropathology~~**neuropathology**: similarities and differences

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**Abstract** Animal models aim to replicate the symptoms, the lesions or the cause(s) of Alzheimer disease. Numerous mouse transgenic lines have now succeeded in partially reproducing its lesions: the extracellular deposits of A $\beta$  peptide and the intracellular accumulation of tau protein. ~~Human mutated~~**Mutated human** APP transgenes result in the deposition of A $\beta$  peptide, similar but not identical to the A $\beta$  peptide of ~~the~~ human senile plaque. Amyloid angiopathy is common. Besides the deposition of A $\beta$ , axon dystrophy and alteration of dendrites have been observed. All of the mutations cause an increase in A $\beta$  42 ~~levels~~**levels**, except for the Arctic ~~mutation that~~**mutation**, which alters the A $\beta$  sequence itself. Overexpressing ~~wild-type~~**wild-type** APP alone (as in the murine models of human trisomy 21) causes no A $\beta$  deposition in most mouse lines. Doubly ~~(APP  $\times$  mutated)~~**(APP  $\times$  mutated** PS1) transgenic mice develop the lesions earlier. Transgenic mice in which BACE1 has been knocked out or overexpressed have been ~~produced~~**produced**, as well as lines with altered expression of neprilysin, the main degrading enzyme of A $\beta$ . The APP transgenic mice have raised new questions concerning the mechanism of neuronal loss, the accumulation of A $\beta$  in the cell body of the neurons, inflammation and gliosis, and the dendritic alterations. They have allowed ~~to gain~~ some insight ~~to be~~**gained** into the kinetics of the changes. The connection between the symptoms, the lesions and the increase in A $\beta$  oligomers has been found ~~to be~~ difficult to unravel. Neurofibrillary tangles are only found in mouse lines that overexpress mutated tau or human tau on a murine tau ~~+/-/-~~ background. A triply transgenic model (mutated APP, PS1 and tau) recapitulates the alterations seen in AD but its physiological relevance may be discussed. A number of modulators of A $\beta$  or of tau accumulation have been tested. A transgenic model may be analyzed at ~~least at~~ three levels ~~at least~~ (symptoms, lesions, cause of the ~~disease~~**disease**), and a reading key is proposed to summarize this analysis.

## Introduction

The extracellular accumulation of A $\beta$  peptide in the core of the senile plaque and the intracellular accumulation of tau protein as neurofibrillary tangles and neuropil threads are ~~to-day~~today considered the two molecular and morphologic signatures of Alzheimer disease (AD), mandatory for its diagnosis [16]. The neuronal loss does not belong to the diagnostic ~~criteria~~criteria, but has been also considered an important pathological component that should be replicated in a good model of AD. A $\beta$  peptide, in its native state, is weakly soluble (a third of its amino-acids -AA-sequence is hydrophobic); it forms dimers, trimers, and in general oligomers. It may aggregate and appear fibrillar at electron microscopy. The aggregates of A $\beta$  peptide finally exhibit the properties of an amyloid substance: it is stained by Congo red and thioflavin S, and is fibrillar at electron microscopy. The extracellular deposits of A $\beta$  peptide may be diffuse or focal. They are said to be amyloid when they have the properties of an amyloid substance, properties that are attributed to a high content of  $\beta$ -pleated sheet structures. A $\beta$  peptide ~~does~~accumulates not only ~~accumulate~~ in the core of the senile plaque but also in the vessel walls (amyloid angiopathy).

Two successive cleavages are necessary to free the A $\beta$  peptide from the amyloid precursor protein (~~APP~~)~~for~~(APP)—for a review see [317]. The first one, the so-called  $\beta$ -cleavage, at the extracellular N-terminus of the A $\beta$  peptide, is due to the beta-site APP-cleaving enzyme (BACE) [42]. It produces a terminal fragment of APP composed of 99 AA called C99. The second cleavage, taking place on APP C99, is performed within a lipid membrane by the  $\gamma$ -secretase complex (made of presenilin1 (PS1) or presenilin 2 (PS2), Pen 2, nicastrin and APH ~~1~~)~~for~~1)—for a review see [340]. The  $\alpha$ -cleavage occurring in the A $\beta$  sequence of ~~APP~~APP prevents the production of A $\beta$ . Four isoforms of APP are expressed in the human, of 695, 714, 751, or 770 amino acid residues. APP 751 and 770 contain a protease inhibitor domain, homologous to the Kunitz type of serine protease inhibitors. In a few families, AD is transmitted as an autosomal dominant trait. The mutations that have been found ~~to be~~ responsible ~~for~~ these cases of familial Alzheimer disease (FAD) are localized on the APP, PS1 or PS2 genes.

The tau pathology is mainly intracellular: accumulation of tau may occur in the cell body (neurofibrillary tangle = NFT), in the dystrophic axons surrounding the amyloid core of the ~~plaque~~plaque, and in the neuropil threads, which are mainly dendrites. At electron microscopy, tau protein mainly accumulates as paired helical filaments (PHF).

**Table 1** This table illustrates, with examples, the SLC reading key that classifies the models according to their ~~purpose~~. ~~The reading key does not intend, in any way, to evaluate the quality of the models i.e. the adequacy between the purpose and the result: for instance, the cholinergic depletion may be excellent or poor, the model will remain of the type S1L0C0 because it intends to mimic the signs (whatever the actual results) and does not intend to reproduce the lesions or the cause of the disease. The value of a model is not necessarily linked to the global score: a restricted model that would perfectly mimic the mechanisms of the lesion in an area that is spared in the natural disease (S0L1C0) could have a high scientific value~~

Models	A reading key <del>to</del> for animal models in <del>AD</del> AD: examples				
	Signs (S)	Lesions (L)	Causes (C)		Final score
			Familial	Sporadic	
Targeted brain lesions	1	0	0	0	S1L0C0
Cholinergic depletion	1	0	0	0	S1L0C0
A $\beta$ injection	1 (depends on site of injection)	1	0	0	S1L1C0
Tg APP (mono)	1	1	1	0	S1L1C1 (for FAD) S1L1C0 (for sporadic AD)
Tg APP (multi)	1	1	0	0	S1L1C0
Tg tau (for expression of tau in the spinal cord)	0	1	0	0	S0L1C0
Tg tau (for expression of tau in the limbic system)	1	1	0	0	S1L1C0
Tg APPxtau	1	1	0	0	S1L1C0

The reading key does not intend, in any way, to evaluate the quality of the models, i.e., their adequacy for the purpose of achieving the result. For instance, whether the cholinergic depletion is excellent or poor, a model that intends to mimic the signs (whatever the actual results), and does not intend to reproduce the lesions or the cause of the disease, will be type S1L0C0. The value of a model is not necessarily linked to the global score: a restricted model that would perfectly mimic the mechanisms of the lesion in an area that is spared in the natural disease (S0L1C0) could have a high scientific value. The table also shows that only ~~Familial~~familial Alzheimer ~~Disease~~disease (FAD) has been correctly ~~modeled~~modeled; the cause or causes of sporadic AD ~~being~~are unknown.

Before analyzing in some ~~details~~detail the numerous models of AD that have been proposed in the literature, we would like to consider, in a general way, the aims that are pursued ~~in~~when trying to mimic a human ~~disease—~~and disease—and more specifically a neurodegenerative ~~disease—~~disease in vivo.

Signs, lesions, ~~cause—~~cause: the SLC reading key

Animal models aim at replicating the symptoms, the lesions or the cause of a disease. A ~~“reading key”~~“reading key” relating Symptoms (S), Lesions (L) and Causes (C) with scores 0–1 is illustrated in ~~table~~Table 1. In neurology, the signs and symptoms (for instance, hemiplegia) are principally linked to the topography of the lesions (for instance motor ~~cortex~~cortex), and are only poorly correlated with their nature (for instance both cerebral infarct and ~~tumor~~tumor); in other words, similarity of clinical signs does not mean similarity in pathogenic mechanisms. Destroying the cholinergic system with ibotenic acid will lead to ~~behavioural~~behavioral symptoms that may resemble those of AD and be ~~amendable~~amenable to treatments such as ~~anti-cholinesterases~~anticholinesterases [226]. It is clear, however, that at the symptomatic level (S), therapeutic research ~~can not~~cannot pretend to reach an understanding of the pathological mechanisms. Such a model ~~helps to understand~~can aid our understanding of the symptoms (it ~~will be said here to~~can be ~~S1 i.e. termed~~“S1,” i.e., it reproduces signs and ~~symptoms~~symptoms), but gives no information on the lesions occurring in AD (we will ~~qualified~~qualify it as ~~L0 i.e. giving~~“L0,” i.e., it gives no information on the way that lesions appear and interact) ~~and all the more~~or on the cause of the disease (~~C0~~)(“C0”): it can ~~therefore~~ be classified as S1L0C0.

At the L level, the model attempts to mimic the lesions: for instance, amyloid peptide has been injected ~~in~~into the ~~brain~~brains of living mice in an attempt ~~of understanding~~to understand its neurotoxicity [262,290]. The results of such an experiment will not ~~give~~provide any information on the reason(s) ~~of~~for A $\beta$  accumulation in the extracellular space. The model is of the type S0L1C0. ~~But~~However, it has also been shown that the A $\beta$  oligomers may impede the synaptic functions and be directly implied in the memory dysfunction [321]; it may therefore also explain the signs of the disease (S1L1C0). A more subtle example, as discussed later in this article, is the modelling of the neurofibrillary tangles of AD by ~~a~~ transgenic mice overexpressing mutated tau. There is no tau mutation in ~~AD~~AD, so the model is clearly not adequate to understand the cause of AD (it is ~~to be~~therefore classified as C0). ~~But whatever the way~~But, ~~however~~ the tangles are produced, it may be interesting to understand how they interact with A $\beta$  peptide in transgenic mice which develop amyloid deposits (~~L1C0~~L1C0). When the tangles are located in the limbic system, then the symptoms may mimic those of AD (S1L1C0); in other mouse lines, the expression of tau in the motor neurones was responsible for paralyse [247]: such a model may help to elucidate how the tangles may cause neuronal dysfunction. It does not ~~help~~aid our understanding of the mechanisms responsible for NFT formation in AD nor the clinical signs of dementia (S0L1C0).

Finally, at the C level, the model attempts to ~~re-construct~~reconstruct the biological mechanisms responsible for the disease, starting from its cause(s). Transfecting a mutated human APP experimentally reproduces the cause of familial Alzheimer disease, ~~due to~~ APP mutation. Some ~~lesions~~lesions similar to those seen in ~~the human~~humans are found in these mouse lines, which may therefore be classified as L1C1. The connection with the symptoms is far from ~~simple~~simple, and it may happen that these mice do not show the typical clinical signs of AD (S0L1C1).

The ~~3~~three levels (S, L, ~~&~~and C) are independent: lesioning the cerebral cortex by an ischemic lesion may, for instance, mimic the symptoms of dementia; it will have little to do ~~both~~ with ~~both~~ the lesions and ~~with~~ the molecular mechanisms of AD: it is a S1L0C0 model. Introducing ~~in the mouse~~ a mutated APP gene ~~into the mouse~~ may mimic familial Alzheimer disease (S1L1C1 for ~~familial AD~~AD), but it could well be that the mechanism has nothing to do with the mechanism of sporadic AD (it is then classified as S1L1C0 or even S0L1C0 as far as *sporadic* AD is concerned). It should be stressed that the cellular mechanisms which lead to A $\beta$  and tau ~~accumulation~~accumulation,

and eventually to neuronal ~~death~~death, could be replicated in neurons located outside the cerebral cortex: the pathology could for instance be fully reproduced in the motor neurone. In such a hypothetical example, the mechanism would be elucidated although the animals would not exhibit the symptoms and signs of the disease (~~S0L1C1~~) ~~or~~(S0L1C1), and possibly not even exhibit the lesions that are presently considered ~~as to be~~ the mandatory stigmata of the disease (~~S0L0C1~~)—~~see table~~—(S0L0C1)—~~see~~ Table 1 for examples.

#### Scope of this review

Which animal models are to be reviewed here? Several ~~procedures—some~~procedures—~~some~~ of which are listed ~~below~~—~~have~~below—~~have~~ been devised in the past to mimic AD in the animal. Destruction has been used to produce the cortical or subcortical symptoms of AD. We will not deal with these models that clearly belong to the S level. The reproduction of the lesions by exogenous chemicals ~~have~~has been attempted: the neurofibrillary tangles (NFT) caused by ~~aluminium~~aluminum have been shown to be actually an accumulation of neurofilaments (and not of tau) [185,225]. Injection of A $\beta$  peptide may induce some clinical signs [227,289] or, under certain conditions, accelerate the pathological process in a transgenic ~~mouse—see~~mouse—~~see~~ later and [111]—~~but~~—~~but~~ it does not directly reproduce the lesions of the disease [99]. Spontaneous animal diseases, resembling AD, have been looked for: old monkeys [245] and old bears [66] for instance, develop plaques and tangles; plaques have been seen in numerous species, noticeably in old dogs [62,69], old cats [68], and in mouse lemurs (~~Microcebus murinus~~)(*Microcebus murinus*) [78]. No model has appeared sufficiently practical to be of common use.

The real breakthrough came from the transgene technology. Transgenesis made it possible, probably for the first time, to reproduce specific neurodegenerative lesions. Mice have ~~been~~ overwhelmingly ~~been~~ used and this review will principally deal with transgenic mice. Recently transgenic rats have been generated [96] with the aim of improving the behavioural analysis. Space is insufficient to deal with invertebrates models: transgenic drosophilae expressing beta-amyloid peptides have been devised to screen therapeutic targets [67]; the naturally lacking  $\gamma$ -secretase activity has been reconstituted in the yeast *Saccharomyces Cerevisiae*~~cerevisiae~~ [92]; the nematode *Caenorhabditis Elegans*~~elegans~~ has also been used to elucidate the physiological role of AD molecular protagonists [134]. Flies, yeasts, and worms play the role of “~~gene factories~~”; “gene factories,” which are particularly useful ~~to study proteins~~for studying protein interactions and ~~to unravel~~unraveling molecular pathways. They are ~~however~~however, too far ~~away~~ from the neuropathology point of view, ~~centred~~centered on the lesions, to be fully covered in this review.

*In vitro* models have been used to unravel the physiopathological mechanisms involved in AD. ~~‡~~This is not the place ~~here~~ to ~~analyse~~analyze the studies based on the hypothesis of a direct toxicity of A $\beta$  peptide on the cell. In this paradigm, the effect of an experimental manipulation is usually tested by comparing neuronal death in control and experimental ~~situation~~.situations. Cell cultures have also been used to elucidate the subcellular topography of the secretase activities. BACE is located in endosomes and also at the cell membrane [142]; Presenilin 1 immunoreactivity is found in the endoplasmic reticulum, while the gamma-cleavage seems to take place downstream of the ER (~~pre-senilin~~—“spatial paradox”)-(the presenilin “spatial paradox”). The production of A $\beta$ 42 (but not of A $\beta$ 40) appears to take place in the endoplasmic reticulum/intermediate compartment [63] ~~while~~while, A $\beta$ 40 is exclusively produced in the ~~trans-Golgi~~trans-Golgi network [114]. Primary cultures of hippocampal slices have been extensively used to study the electrophysiological consequences of A $\beta$  oligomers (see later).

This paper is focused on transgenic mice. The literature has ~~rapidly~~ grown rapidly on this ~~topic~~topic, and we have been forced, in many instances, to limit our subject and our analysis of the literature. The reader is referred to excellent reviews on the subject [102,129,214,215,285,313]. We have deliberately not reviewed the effects of active or passive A $\beta$  immunotherapy on Tg mice, ~~as since this~~ subject ~~much~~is far too ~~large~~extensive for this review.

## Specific problems raised by the pathology of transgenic mice

Transgenesis raises specific difficulties and questions. The number of transgenes that have been inserted and their ~~sites~~ sites of insertion are uncontrolled. The expression of the gene may reach high values that trigger ~~defence~~ cellular defence mechanisms that ~~will give only~~ provide little information on the natural role of the transgene itself. The topography of the protein expression and its course during development ~~largely~~ largely depends on the promoter. Some defects may be related to anomaly of development and ~~may~~ be unrelated to the overexpression of the protein in the ~~adult~~—adult—a problem which can be solved ~~by~~ through the use of inducible systems of expression (see later) or by the use of gene knock-down by siRNA [274]. The genetic background may substantially modify the pathology [46], and uncontrolled results may be related to outbred lines. The transgenic animals should, if necessary, be backcrossed for multiple generations to obtain inbred lines. The incidence of gender has been mentioned in several studies: amyloid deposition has been found to be more extensive in female APP mice [323]. Pharmacological treatments with intended anti-A $\beta$  effects have been found to have different (even opposed) effects in male and female transgenic ~~mice~~ ~~e.g. mice, e.g.~~, [240], reinforcing the contention that gender is a variable to take into account in the analysis of murine models.

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## The transgenic models of A $\beta$ accumulation

After the identification of the A $\beta$  peptide, initially in vessels of trisomy 21 patients and then in senile plaques of AD cases [105,208,341], several teams looked for ~~“the”~~“the” mutation responsible ~~of~~ for the rare cases of familial Alzheimer disease (~~FAD~~)—only(FAD)—only to realize that not one but numerous mutations were actually able to cause the disease. Mutations are indeed located not only in the APP gene [52,106], from which the A $\beta$  peptide is cleaved, but also in the ~~gene~~genes of presenilin 1 or 2 [4,259,280] that are directly involved in A $\beta$  production from APP.

It is ~~to day~~now clear that there is not one but several A $\beta$  peptides, with a C-terminal heterogeneity: some isoforms end at the AA 40, ~~other~~and others at the AA 42 or even at AA 43, 45, 46 or 48 [248]; the cause of this heterogeneity is still unknown. Several A $\beta$  species are N-truncated and were shown to be the main A $\beta$  species in some APP mutations [173,275]. All of the mutations that have been tested, when transfected in cellular models, induce an increase in the A $\beta$ 42/A $\beta$ 40 ratio [72], with the noticeable exception of the Arctic mutation ~~involving~~ directly involving the A $\beta$  sequence itself [55]. All mutations induce an overproduction of A $\beta$  with the noticeable exception of the mutation ~~V715M~~V715M, in which, however, the ratio A $\beta$ 42/A $\beta$ 40 is increased [6]. Transfecting the APP gene induces an overproduction of the ~~protein~~protein, and APP overproduction may be sufficient to increase A $\beta$  peptide secretion: both the  $\beta$  and the  $\gamma$  enzymatic activities do not appear to be rate-limiting. However, as we shall see, APP has to be mutated to produce a quantity of A $\beta$  sufficient to cause visible changes.

Mutations of the gene of tau proteins are not associated with AD but with fronto-temporal dementia [284]. It is therefore logical to consider that AD pathogenesis is related to a change in APP rather than in tau metabolism. This conclusion is formalized as the ~~“cascade hypothesis”~~that“cascade hypothesis,” which states that the excessive production of A $\beta$  peptide is the cause of a cascade of reactions that lead to tau pathology and neuronal death [116,~~117,118,~~119].

## Various APP transgenic models

The three human isoforms of APP (hAPP) (695, 751, and 770 amino-acids) have been used as transgenes. The mutations of the APP gene that have been used most often ~~used~~ are ~~labelled~~labeled by the place where they have been identified: Swedish (which is made of two contiguous mutations), London, and ~~Indiana, respectively K670N~~Indiana



(K670N & M671L, V717I and ~~V717F~~V717F, respectively, with the numbering corresponding to the longest APP isoform-isoform). The hAPP gene has been driven by various ~~promoters: PDGF,~~ promoters—PDGF, Thy-1 or Thy-1.2 (~~neuron-specific~~), (neuron-specific), and hamster PrP (not ~~only neuronal~~)—that just neuronal—which allows its exclusive or preferential expression in the central nervous system. A ~~large,~~ large but certainly ~~incomplete,~~ incomplete list of the transgenic lines pertaining to AD ~~is to can~~ be found on the ~~site of~~ Alzforum website (<http://www.alzforum.org/res/com/tra/>).

### *The APP singly transgenic lines*

Seventeen amino acids differ in mouse and human APP; three of them are located in the A $\beta$  sequence (Arg 5 Gly, Tyr 10 Phe, His 13 ~~Arg—the~~Arg—the first AA is the human one). However, increasing the level of mouse APP does not cause A $\beta$  deposition. Transfection of human APP is necessary [153], and the trisomy16 murine model (where no A $\beta$  deposition is found) suggests that hAPP has to be mutated to obtain a reliable and abundant deposition.

*Initial attempts* Now that numerous mouse lines with A $\beta$  deposits have been produced, it is interesting to look back at the first, largely ~~unsuccessful~~unsuccessful, attempts to develop an Alzheimer model [215]. After unconfirmed results of Alzheimer pathology in ~~transgenic~~transgenics expressing the C-terminal part of APP [161] or the A $\beta$  peptide under the promoter of APP [332], several lines were generated with various techniques. The sequence limited to the A $\beta$  peptide itself, under the promoter of the light chain of neurofilament, was neurotoxic. A $\beta$  remained intracellular and caused apoptotic cell death [179]. Since A $\beta$  ~~being~~is partly hydrophobic, its cellular fate when synthesized outside a cell membrane was probably not physiological. The pathogenic effects of its overproduction were probably not directly linked to the pathogenesis of AD. Several attempts were made to introduce ~~wild-type~~wild-type human APP ~~in~~into transgenic mice. Several transgenic lines were produced with a transgene that comprised the 100 AA of the C-terminal part of APP [160,228]. A weak A $\beta$  accumulation was found in the cell body and the neuropil; C100 was also found to aggregate in vesicular structures of the cytoplasm [160]. ~~Long-term~~Long-term potentiation (LTP) was impaired [228], but the extracellular deposits of A $\beta$  were limited or absent. In the APP-C99 (Tg 13592) mouse line, the signal sequence and the 99 amino-acids C terminal fragment (C99) of APP is overexpressed under a cytomegalovirus enhancer/ $\beta$ -actin promoter [97]. The expression is detected in many ~~tissues~~tissues, and A $\beta$  deposits are detected only in the muscle in aged ~~animal.~~animals. The plasma concentration of A $\beta$  peptide is increased ~~17-times.~~17-fold. There are no deposits in the brain. The mice exhibit hypoactivity and spatial learning deficit. This transgenic line indicates that the increase in plasma A $\beta$  peptide concentration does not produce amyloid in the ~~brain~~brain, and strongly suggests that the production of A $\beta$  peptide takes place in the brain of FAD patients rather than at the periphery.

A yeast artificial chromosome containing ~~wild-type~~wild-type APP did not induce any visible changes. A YAC containing the human APP gene encoding APP harboring the Swedish mutation, the London mutation or a combination of the two increased the ~~A $\beta$ 42—A $\beta$ 40~~A $\beta$ 42/A $\beta$ 40 ratio and decreased the concentration of  $\alpha$ -secretase derivatives [184]. A $\beta$  deposits and neuritic abnormalities were found in the olfactory cortex and olfactory bulb in ~~14 months old~~14 month-old animals which expressed a YAC containing APP with the Swedish mutation, mated to homozygosity [172]. A human APP 695 transgene with the London ~~mutation,~~mutation driven by the ~~neuron-specific~~neuron-specific enolase was not associated with any microscopical changes (probably because the levels of A $\beta$  were not sufficient) [203]. These first attempts indicated that the A $\beta$  sequence alone was ~~inefficient,~~that inefficient; the whole sequence of APP had to be ~~expressed~~expressed, and ~~that~~ only mutations were able to cause a significant increase ~~of~~in A $\beta$  42. The YAC technology was ~~fruitful~~fruitful, but lesions were observed in limited amounts and only in old animals. The NSE promoter was not powerful enough to drive A $\beta$  secretion to the threshold level necessary to cause lesions.

A large number of hAPP singly transgenic mice with significant changes have ~~thereafter~~since been produced; only the singly transgenic mouse lines that have been most studied in the literature are listed below.

*The PDAPP transgenic line*

The transgene of the first mouse line with significant pathologic accumulation of  $A\beta$  peptide was a cDNA minigene bearing the sequence of human APP (hAPP) carrying the Indiana mutation (V717F) with portions of APP introns 6–8. The presence of introns 7 and 8 allowed the alternative splicing of exons 7 and 8, and the expression of the 695, 751 and 770 APP isoforms. APP expression was driven by the PDGF promoter [98]. This PDAPP transgenic line has been extensively studied. From the age of ~~6 months~~six months, the heterozygous mouse develops visible extracellular deposits of  $A\beta$  peptide in the ~~hippocampus~~hippocampus, and at ~~8 months~~eight months in the isocortex [98,146]. Some deposits are amyloid (Congo red and thioflavin S positive).  $A\beta$  peptide is also found in the vessel walls.



*The Tg2576 mouse line* The Tg2576 mouse line [137] overexpresses the 695 isoform of human APP with the Swedish double mutation (K670N/M671L) under the control of the hamster prion protein promoter. A $\beta$  diffuse and focal deposits are found at 9–11 months of age in the heterozygous animal.

*The APP23 mouse line* In the APP23 mouse line, developed by Novartis Pharma, the 751 isoform of human APP with the double Swedish mutation is expressed under the control of a mouse Thy-1.2 promoter [292]. ~~(The)~~ (the same cDNA under the control of a human Thy-1 promoter had no pathology). There ~~are~~ diffuse and congophilic deposition of A $\beta$  peptide in parenchyma and vessels from ~~6~~ six months of age.

*Line C3–3* ~~H~~This is also an APP bearing the Swedish double ~~mutation~~ mutation, which is overexpressed in this mouse line. The chimeric mouse/human APP with the Swedish mutation K670N/M671L contains a humanized A $\beta$  domain. The promoter is the mouse prion promoter. The mice do not develop plaques until 18 months of age [30,31].

*The Tg CRND8 mouse line* The Tg CRND8 mouse bearing both the Swedish double mutation and the Indiana mutation (hAPP695 K670N, M671L + V717F), under a hamster prion promoter, develops plaques ~~at~~ as ~~early~~ soon as ~~3 months~~ three months of age [57]. The high A $\beta$  concentration and the highly increased A $\beta$ 42/A $\beta$ 40 ratio explain why this model is particularly aggressive.

*The hAPP H6, J9 and J20 hAPP lines* Several Tg lines expressing, at various levels, ~~wild-type~~ wild-type or mutated hAPP were produced under a ~~platelet-derived~~ platelet-derived growth factor beta chain promoter (PDGF). A summary of the most commonly used of these Tg animals is given in [222] ~~p 4052~~ (p. 4052). We just mention here the lines that we will consider later: the J9 and J20 lines, ~~as~~ like the Tg CRND8 line, express hAPP with the Swedish and the Indiana mutation. In these lines, the human transgene is the isoform 770. The J9 line (~~“hAPP<sup>low</sup>”~~) (“hAPP<sup>low</sup>”) expresses a moderate level of neuronal APP and A $\beta$ ; the level of expression is high in the J20 line [56]. Line H6 ~~also~~ expresses hAPP with the Indiana mutation ~~also~~ under the control of a PDGF promoter [344].

*The APPDutch line* The E693Q mutation of APP induces a massive amyloid angiopathy, ~~as~~ described in Dutch patients. The disease has been replicated by generating a mouse line expressing hAPP751 with the ~~with~~ E693Q mutation under a murine Thy1.2 promoter. Vascular accumulation of A $\beta$  with ~~haemorrhages~~ hemorrhages and inflammation have been observed in these mice [128].

*The ARC6 and ARC48 lines* The Arctic mutation (E22G) is located in the A $\beta$  sequence; it stimulates A $\beta$  fibrillization without changing the A $\beta$ 42/A $\beta$ 40 ratio. The transgene is a minigene containing APP with the Arctic mutation and also the Swedish and Indiana mutations, under the control of the platelet-derived growth factor  $\beta$ -chain promoter [54].

Data obtained from the comparison of different mouse lines indicate that the onset and the severity of the amyloid deposits are directly linked to the level of A $\beta$ 42 peptide. ~~Sturchler-Pierrat~~ Sturchler-Pierrat et al., in parallel with the APP23, developed a line in which only a ~~2-fold~~ twofold overexpression of human APP bearing the Swedish and the Indiana ~~mutation~~ mutations was obtained. A $\beta$  deposition was seen later than in the APP23 and there was ~~but~~ little amyloid formation [292]. In a series of different mouse lines with an hAPP 751 transgene bearing the Swedish and the London mutations, the progression of the pathology appeared ~~to be~~ directly linked ~~with~~ to the ~~level of~~ A $\beta$ 42 concentration [257], the level of A $\beta$ (1–40) being higher in mice that did not show any amyloid deposits. A high level of A $\beta$ 42 is a necessary condition, but it is not sufficient: Mucke et al. generated different APP transgenic lines under the

same promoter (PDGF); they noticed that the overexpression of ~~wild-type~~wild-type human APP, even if it increased the level of A $\beta$ 42, was insufficient to cause plaque ~~formation—formation—~~which was observed only when the APP transgene carried a pathogenic ~~mutation,mutation~~ known to be responsible for familial AD [222]. However, the late occurrence of A $\beta$  deposits was mentioned in two ~~lines,lines~~ (as briefly and incompletely described in the ~~literatur-e,literature~~) in which human APP, without mutation, was overexpressed under the control of a NSE [130] or a Thy-1 promoter [128]. Only the overexpression of ~~APP751—,but~~APP751, not ~~of~~ APP695, was able to induce A $\beta$  deposition in the first model.

### *Trisomy 21 models*

Chromosome 21, which is ~~present~~ in a triple dose in Down syndrome, contains the APP gene, ~~explaining~~which ~~explains~~ why AD lesions are almost constant at a relatively early age. An exceptional patient with a partial trisomy 21 that did not include the APP gene did not develop AD [244]. On the other hand, microduplication of the APP gene, inducing AD with prominent amyloid angiopathy, has recently been identified [261]). Models of trisomy 21 (trisomy 16 in the mouse) have been generated and ~~give~~provide information not only on the role of ~~the~~ APP gene but also ~~of~~ its contiguous genes in the pathology. Two segmental trisomy 16 models, Ts65Dn and Ts1Cje, have contrasted consequences. In the Ts65Dn mouse [251], a large segment of chromosome 16 including the APP ~~gene,gene~~ is in three ~~copies~~copies, while the segment in triplicate in the Ts1Cje mouse is smaller and does not include the APP gene nor the gene of the superoxide dismutase 1 (SOD1) [264]. Increased levels of APP mRNA and of the protein itself have been detected in the Ts65Dn mouse in the striatum by 6–8 months of age, and in the hippocampus and parietal cortex by 13–16 months of age. A $\beta$ 42 levels have been found to be increased at ~~6-months~~six months. At this age, the basal forebrain cholinergic neurons (BFCN) start degenerating [141], a degeneration that is related to impaired retrograde transport of NGF [64,265]. Neither total tau nor tau phosphorylated on the serine 199 are elevated in the Ts65Dn mice [140]. As expected, the level of A $\beta$ 42 is normal in the Ts1Cje mouse line (which has the normal two copies of the APP gene) and there is no degeneration of the BFCN. However, and quite unexpectedly, abnormal phosphorylation of tau has been detected in this mouse line without tangle formation [281]. In the ~~“transchromosomic”~~“transchromosomic” 21 model (Tc1), an almost complete human chromosome 21 has been incorporated ~~in~~into the mouse genome [236]. Few data concerning APP metabolism are presently available.

Early endosomal alterations, the earliest known pathology detected in sporadic AD and ~~DS-develops~~DS, develop before A $\beta$  is deposited and as soluble A $\beta$  increases [50]. In the basal forebrain of Ts65Dn mice, neurons develop enlarged endosomes at ~~2-months~~two months. There is no enlargement of the endosomes in the Ts1Cje mice (no APP overexpression) ~~and/or~~ in transgenic mice overexpressing APP751 with the Swedish double mutation alone or in combination with the London mutation [49]. The cause of endosome enlargement ~~remains~~is still to be fully elucidated.

### *Presenilin transgenic mice*

Mutated human PS1 or PS2, when expressed alone, do not induce any detectable ~~lesion~~lesion, although they increase the level of A $\beta$  peptide [211,239,268]. The ~~behavioural~~behavioral impairment is modest [154,183]. The mutated PS1 transgene, however, disturbs calcium homeostasis in the endoplasmic reticulum [211]. It has furthermore been recently shown that a mutated human PS1 transgene altered the fast axonal transport and induced tau hyperphosphorylation [189].

### *Doubly transgenic mice*

The  $\beta$ - and  $\gamma$ -secretase pathway APP and ~~Bace~~BACE ( $\beta$ -secretase)

APP plus ~~Bace~~BACE1

~~BACE~~BACE1 cleaves APP at AA 1 of the A $\beta$  peptide but also at AA 11, producing N-truncated A $\beta$ . BACE1 transgenic mice (with the promoter of the Ca<sup>2+</sup>/calmodulin-dependent protein kinase II gene = CaMKII) have an increased turnover of serotonin and ~~exhibit~~ bolder ~~behaviour~~behavior than control littermates [120]. hAPP mice have been crossed with mice overexpressing ~~BACE~~BACE1. The BACE transgene increased the level of A $\beta$  but also ~~that~~ of the C-terminal fragments of APP [27]. The coexpression of ~~BACE~~BACE1 in a transgenic APP line increased the density of diffuse and focal deposits of A $\beta$  peptide, but, unexpectedly, dramatically decreased the severity of amyloid angiopathy. This was considered ~~the~~a consequence of the abundance of N-truncated A $\beta$  species. In this hypothesis, the N-truncated A $\beta$  peptide accumulates preferentially in the parenchyma, while the full-length A $\beta$  peptide may be drained and accumulates in the vessels [331]. In another study, BACE1 co-expression (murine Thy1 promoter) with hAPP decreased the level of A $\beta$  and of ~~APP~~APP, but worsened the severity of the neurodegeneration, ~~which~~ is possibly ~~the~~a consequence of the accumulation of APP C terminal fragments (CTF) [258].

APP minus ~~Bace~~BACE1

~~Mice, knock-out~~Mice knocked-out for ~~BACE~~BACE1 are viable and fertile and do not produce A $\beta$  [199]. They are timid and less exploratory than the controls [120]. Mutation of the  $\beta$ -secretase cleavage site (M671I) on APP also eliminates ~~the~~ production of human A $\beta$  [223]. Lowering BACE1 levels using lentiviral vectors expressing siRNAs ~~targeting~~that target BACE1 reduced amyloid production and ~~the~~ neurodegenerative and behavioral deficits in APP transgenic mice [282]. Crossing BACE1 KO mice with PDAPP mice [212] or ~~with~~with TG2576 mice [199] prevented the pathology. Loss of BACE1 function rescued the ~~behavioural~~behavioral alterations [212]. ~~Even~~The effect was even ~~spectacular~~ in PDAPP mice heterozygous for BACE1, ~~the effect was spectacular~~ although the decrease in A $\beta$  42 was relatively modest (~~-12%~~)(-12%) [212]. These results suggest that inhibition of BACE could be a therapeutic target. Unfortunately, other results indicate that BACE ~~+/+~~-/-  $\times$  PDAPP mice have unexpected sensorimotor impairments, spatial memory deficits, and display ~~seizures~~—a seizures—a phenotype that could prevent the use of inhibitors of BACE [168].

APP and ~~Presenilins~~presenilins ( $\gamma$ -secretase)

APP plus ~~Presenilin~~presenilin

The co-transfection of human mutated (M146L or M146V) presenilin 1 significantly lowers the age at which the first plaques are detected [89,131,216], most probably by increasing the quantity of ~~secreted~~A $\beta$ 42.A $\beta$ 42 ~~secreted~~. Wild-type PS1 or PS2 has no effect [89]. In C3-3 ~~mice,~~mice crossed with mice expressing a mutant PS1, the A $\beta$  deposits are visible at ~~9 months~~nine months (instead of 18) [30,31]. The PSAPP line has been obtained by crossing Tg2576 mice with mice expressing human PS1<sub>M146L</sub>. Amyloid deposits are present at ~~6 months~~(~~9 months~~six months (nine months in the Tg2576 mouse line). In a APP<sub>SL</sub>PS1<sub>M146L</sub> mouse model developed by Sanofi-Aventis, a human APP751 gene carrying both the Swedish and the London ~~mutation~~mutations (K670N/M671L and V717I) under the control of the Thy-1 promoter is associated with a human mutant gene of presenilin-1 (PS-1 M146L) under the HMG-CoA reductase promoter (allowing a preferential cerebral expression). An intracellular accumulation of A $\beta$  peptide is visible at ~~2 months~~two months, and A $\beta$  plaques appear as early as ~~3 months~~three months [26,186]. A similar mouse ~~line,~~line with the M233T/L235P mutations knocked in the PS1 gene (APP<sub>SL</sub>PS1<sub>K1</sub>) develops a very aggressive form of the disease but also a prominent neuronal loss in the CA1 sector [48].

The coexpression of hAPP with the Swedish double mutation (K670N/M671L) and ~~that~~ of PS1 with the L166P mutation under the control of a neuron-specific Thy1 promoter element (APPPS1 mice) dramatically lowers the age at which the first lesions are ~~visible~~—visible: cerebral amyloidosis starts at ~~6–8 weeks~~6–8 weeks, and the number of microglial cells increases ~~3-fold~~threefold from ~~1~~one to ~~8 months~~eight months. Neuronal loss appears minimal [249].

The 5XFAD model was devised to accelerate A $\beta$  deposition [231]; these APP/PS1 double transgenic mice coexpress five FAD mutations [APP K670N/M671L (Swedish) + I716V (Florida) + V717I (London) and PS1

M146L&L286V]. Intracellular accumulation of A $\beta$ 42 is seen at 1.5 months of age and amyloid deposition begins at ~~2 months~~ two months.

~~A~~The deletion of exon 9 in presenilin 1 increases, in man, the secretion of A $\beta$  peptide and is associated with the occurrence of large and homogeneous senile plaques that are only weakly congophilic (the so-called ~~cotton~~“cotton wool ~~plaques~~ plaques”). The occurrence of the lesions is accelerated in the mouse when an hPS1 gene with ~~a deletion of the~~ exon 9 ~~deleted~~ (line S9) is coexpressed with a hAPP gene with the APP Swedish mutation (line ~~C3-3~~C3-3), yielding an APP<sup>swe</sup>/PS1<sup>dE9</sup> line [100,191]. The first A $\beta$  deposits are detected at the age of 4–5 months. The E9 deletion of the PS1 gene, rather than inactivating the gene, induces a gain of function.

#### *APP minus ~~Presenilin~~presenilin*

The PS1 knockout (KO) mice are not viable. They have skeletal and CNS deficits (hemorrhages, deficient ~~neu-~~~~rogenesis~~ neurogenesis) which could partly be due to the role of the gamma-secretase in Notch signaling [279]. Using a loxP/Cre-recombinase strategy, Dewachter et al. succeeded in generating a post-natal, ~~neuron-specific~~ neuron-specific, PS1 KO mouse. The absence of presenilin 1 prevented the formation of A $\beta$  peptide deposits [77]. However, a cognitive deficit (object recognition test) was still present in the hAPP [V717I] ~~\*x~~ PS1 ~~+/-/-~~ mice, a deficit that the authors attributed to the increase in APP C99 (the product of ~~the~~ BACE cleavage of APP). The potential ~~toxic~~ ~~role~~toxicity of C99 has been tested in the Tg 13592 line, in which spatial learning deficit has been observed in the absence of brain A $\beta$  deposits.

*The  $\alpha$ -secretase pathway* The  $\alpha$ -secretase cleaves APP in the A $\beta$  sequence. ~~ADAM10~~ ~~A~~ADAM10—A Disintegrin And ~~Metalloproteinase~~ ~~is~~Metalloproteinase—is presently the best candidate ~~as~~for the enzyme responsible for the  $\alpha$ -secretase activity [170]. The ~~wild-type~~wild-type human ADAM10 gene, in a mouse line carrying hAPP with the London mutation, increased the secretion of sAPP, reduced the concentration of A $\beta$  ~~peptide~~peptide, and prevented the formation of A $\beta$  peptide deposits. ~~On the contrary~~In contrast, the expression of an inactive mutant of ADAM10 worsened the pathology [243].

#### *A $\beta$ degradation* Neprilysin

Neprilysin (or neutral endopeptidase 24.11 = NEP or CD10 or enkephalinase) is thought to be at least partly responsible for the ~~degrading~~degradation of A $\beta$  peptide. This metalloendopeptidase is inhibited by phosphoramidon and thiorphan [149]. Transgenic expression of neprilysin improves the pathology and the ~~behaviour~~behavior in an ~~APPxPS1~~APP  $\times$  PS1 mouse line with ~~a~~ Swedish and Indiana ~~mutation~~mutations [242]. A lentiviral vector expressing human neprilysin decreases ~~by half~~ the density of plaques ~~by half~~ [205].

Chronic infusion of thiorphan in the rat induces A $\beta$  deposition [149]. Increased concentration of A $\beta$  peptide is observed in ~~NEP~~ ~~-~~NEP ~~-/-~~ mice [91,148]. Amyloid-like deposits ~~in addition to~~and signs of neuronal degeneration have been observed in aged neprilysin-deficient mice [201]. Loss of NEP function in APP mice markedly increased hippocampal amyloid plaque burden, and led to the development of amyloid angiopathy. Even a ~~50%~~50% reduction ~~of~~in NEP activity was sufficient to increase amyloid neuropathology [95]. ~~APPxNEP-KO~~APP  $\times$  NEP-KO mice have been shown to develop synaptic alterations and cognitive deficits, presumably in relation ~~with~~to increased levels of A $\beta$  oligomers [138].

#### *Inducible model*

The difficulty ~~met~~involved in solubilizing amyloid, whatever its composition, ~~left open~~meant that the question ~~of~~regarding the course of the disease if ~~the~~ A $\beta$  accumulation is ~~just~~ stopped but ~~the~~ amyloid ~~remains~~stays in ~~place~~place ~~remained open~~. An inducible model made it possible to study the evolution of the plaques after the ~~hAPP695~~Swedish/

~~Indiana transgene~~,hAPP695 Swedish/~~Indiana transgene~~ had been inactivated. It appeared that the amyloid pathology did not progress, but it did not ~~regress~~.regress either. The amyloid core produced the same inflammation and was surrounded by dystrophic neurites [152].

### Conclusions

The alterations observed in these various mouse models are compatible with a coherent view of APP metabolism: APP is cleaved by BACE1 and the  $\gamma$ -secretase complex to produce A $\beta$  peptide. Higher A $\beta$  levels are observed when either BACE or the  $\gamma$ -secretase activity is increased. When the concentration of A $\beta$  is sufficient, deposits are observed ~~but~~, in the mouse, ~~but~~ only if APP is mutated. Stimulating the  $\alpha$ -secretase pathway (ADAM10 transgenic line) or the degradation of A $\beta$  (NEP transgenic line) improves the pathology and the ~~behaviour~~.behavior.

In the next section we consider, from a pathological point of view, the lesions that are observed in the transgenic lines. We have distinguished the expected ~~alterations, those~~alterations—those that are present in man and absent in the ~~animal, and~~animal—and finally the lesions that ask new questions or suggest new ~~point~~points of ~~views~~.view.

#### *Pathological consequences of the accumulation of A $\beta$ peptide*

To simplify the terminology, the ambiguous term ~~of senile plaque~~“senile plaque” will be avoided as much as possible. The term ~~“diffuse”~~“diffuse” describes the ~~non-amyloid (non-congophilic, non-fibrillar)~~,nonamyloid (non-congophilic, nonfibrillar), large and irregular A $\beta$  ~~deposits~~,deposits; the term ~~“focal”~~“focal” describes the small, spherical, intensely immunoreactive A $\beta$  deposits; and the term ~~“amyloid”~~“amyloid” is used for the deposits that are stained by thioflavin-S or Congo red.

Aspects for which the APP transgenic lines may serve as good models of AD

In many ways the APP transgenic mice mimic the amyloid aspect of Alzheimer ~~pathology~~:pathology.

#### *A $\beta$ production and A $\beta$ deposits*

While APP overexpression remains roughly constant during the ~~lifelines~~ of the APP transgenic mice, the level of A $\beta$  increases with age. In the PDAPP mouse line, for instance, A $\beta$  concentrations increase 17-fold in the hippocampus between the ages of ~~4~~four and ~~8-months~~,eight months, and by 18 months are over 500-fold that at ~~4-months~~four months [158]. From a given age on, the ~~mice~~mice, which produce a large amount of ~~A $\beta$  42~~,A $\beta$ 42, develop visible deposits first in the hippocampus and isocortex and secondarily in some subcortical nuclei. Although the topography of the lesions depends on the transgene promoter, it should be stressed that the deposition exhibits a laminar pattern that suggests that A $\beta$ 42 is secreted in the terminal field of ~~the~~ neurons, probably ~~just~~ as ~~occurs~~ in humans. In some lines, this is particularly striking for the perforant path that links the neurons of layer II of the entorhinal cortex with the external molecular layer of the dentate gyrus [293]. ~~Section of~~Sectioning the perforant path prevents the formation of the amyloid deposits in the molecular layer of the dentate gyrus [188]. The deposits are Congo red and thioflavin S positive and are made of amyloid fibrils 9–11 nm in diameter, as in AD. The process ~~of the formation of~~by which the amyloid fibrils ~~are formed~~ is not ~~the~~a mechanical consequence of an increase in APP overexpression and A $\beta$  peptide concentration. APP may be overexpressed at higher levels in regions devoid of plaques ~~rather~~ than in areas where they are abundant [158]. It has been shown that A $\beta$  deposition ~~could~~can be dramatically accelerated by the injection of amyloid ~~substance~~substances from older transgenic mice or even from human amyloid. Strangely enough, ~~in a way~~ ~~similar~~somewhat ~~similarly~~ to what has been observed in prion diseases, the fibrils obtained by simply having the synthetic peptides precipitated in solution are not efficient [218,319].



### *Amyloid angiopathy*

Amyloid angiopathy is common in APP transgenic mice [127]. It was a common belief that A $\beta$  deposition in the vessel walls of perforating arteries and subarachnoid vessels ~~were~~ was due to the secretion of A $\beta$  peptide by the smooth vascular muscle cells [338]. ~~Tg~~ Tg mice have demonstrated that this is far from always being true. In some transgenic lines, ~~the~~ amyloid angiopathy appears particularly ~~prominent~~ ~~as prominent~~ as in the line generated by Van Dorpe et al. (695 isoform of ~~hAPP—London~~ hAPP—London mutation ~~V717I~~, V717I; murine Thy1 promoter) [315] and in the line APP23 (isoform 751 of APP with Swedish mutation; murine Thy-1.2 promoter) [43]. The role of the A $\beta$ 42/A $\beta$ 40 ratio is an important determinant of the distribution of A $\beta$  in vessels or in parenchyma: the APPDutch mice (E693Q APP751) develop prominent amyloid angiopathy, associated with an ~~increase~~ increased level of A $\beta$ 40. ~~But~~ However, the APPDutch mice crossed with PS1<sub>G384A</sub> Tg mice mainly develop parenchymal deposits, ~~the ratio A $\beta$ 42/A $\beta$ 40 being~~ with an increased ratio of A $\beta$ 42 to A $\beta$ 40 [126]. ~~Since~~ Since the deposition is seen in transgenic lines in which A $\beta$  peptide is expressed under a neuronal promoter, it is highly probable that the ~~peptide~~, peptide produced by the ~~neurons~~, neurons accumulates in the vessel walls [43,315]. This is compatible with the theory put forward by Weller et al. that the A $\beta$  peptide is drained with interstitial fluid through the ~~peri-vascular~~ perivascular space (in a direction opposite to the arterial blood flow) [328]. Recently, A $\beta$  peptide was found in the perivascular space of APP23 mice and also, in small amounts, in ~~wild-type~~ wild-type aged animals. A $\beta$  was colocalized with ~~ApoE~~ ApoE, suggesting that the drainage of A $\beta$  could involve an interaction with ApoE [301].

### *Pathology of synapses*

*Synaptophysin* ~~Immunoreactivity~~ immunoreactivity Loss of synaptophysin immunoreactivity (IR) has been considered to be a hallmark of AD pathology and the best correlate of cognitive deficit [298], an opinion that has, however, been ~~discussed~~ under discussion [79]. The results in the Tg mice have been contradictory. Some studies reported an absence of change: ~~in~~ in the APP23 mouse line, for instance, no loss of synaptophysin IR has been detected despite robust A $\beta$  deposition [28]. The loss may be subtle: in the TG2576 APP mouse line, no loss was initially observed, but rather an increase, correlated with a deficit in synaptic function [165]; a more exhaustive stereological and ultrastructural analysis in the same line found a decrease in the synaptic density of the external molecular layer of the dentate gyrus, in close relation ~~with~~ to the A $\beta$  deposits [87]. Some studies report a reproducible loss of synaptophysin IR. The decrease in density of presynaptic terminals precedes ~~for~~ by several months the extracellular deposition of A $\beta$  peptide in a line H6 (see above) [136]. An age-dependent decrease in synaptophysin IR has been documented in the PDAPP mouse line [84]. Mucke et al. have generated several mouse lines expressing either ~~wild-type~~ wild-type or mutated human APP. At the same level of expression of hAPP, extracellular deposits of A $\beta$  peptide are observed only when APP is mutated, even when the level of A $\beta$ 42 is high. The density of synaptophysin IR is ~~even~~ found to be decreased ~~even~~ in mice expressing ~~wild-type~~ wild-type APP without A $\beta$  deposits. It is inversely correlated with the level of ~~A $\beta$  42~~ A $\beta$ 42, but it is not necessarily associated with a high plaque load or with a high level of APP expression [222]. Synaptic alterations can thus be seen in the absence of extracellular deposit of A $\beta$  peptide. Moreover, ~~age-related~~ an age-related decrease in synaptophysin IR has been observed in PS1 singly transgenic mice [263]. Presynaptic markers synaptophysin and ~~syntaxin~~, syntaxin as well postsynaptic density-95 decreased with age in the 5XFAD model [231].

The density of dendritic spines decreases in the CA1 sector of PDAPP and of Tg2576 before A $\beta$  deposition [187]. It has been suggested that the loss of dendritic spines could be related to the toxicity of A $\beta$  oligomers. The density of spines of rat pyramidal neurones in culture was decreased after exposure to picomolar levels of soluble oligomers of A $\beta$  peptide. This effect is mediated by ~~NMDA-type~~ NMDA-type glutamate receptor and is reversible [278]. ~~A $\beta$ -derived~~ A $\beta$ -derived oligomers (ADDLs) selectively ~~binds~~ bind to postsynaptic densities of presumably excitatory neurons (sparing the inhibitory GABAergic ~~ones~~, ones) in cultures of highly differentiated hippocampal neurons. This

binding is associated with a decrease in membrane expression of NMDA and EphB2 receptors and with the appearance of abnormally long thin spines [177].

While the effect on spines is probably caused by ~~A $\beta$ -soluble~~A $\beta$ -soluble oligomers, larger changes observed on dendritic trees seem to be more directly correlated with fibrillar amyloid deposits. In the Tg2576 transgenic line, the dendritic density is diminished within the boundaries of amyloid-beta plaques, with the greatest loss (about 80%) in the thioflavin S positive cores. The processes are abnormally curvy [190]. In the same line, in vivo imaging using multiphoton confocal microscopy reveals spine loss and shaft atrophy of dendrites near A $\beta$  deposits [304].

In conclusion, the data ~~of~~in the literature indicate a regular drop in the presynaptic marker synaptophysin in the APP transgenic mice; this decrease may be seen in the absence of A $\beta$  ~~deposit~~deposits (but with high ~~con-~~centrationconcentrations of A $\beta$ 42)A $\beta$ 42), and has been also noticed in PS1 transgenic mice. The fibrillar deposits of A $\beta$  peptide, on the other hand, alter the dendrites.~~Long-term~~**Long-term potentiation and A $\beta$  oligomers**

~~Long-term~~Long-term potentiation (LTP) is an enhanced synaptic transmission observed in synapses that have previously been stimulated. It is studied ~~with~~through electrophysiological means ex vivo (brain slices) or in vivo. LTP, which can be considered ~~as to be~~ a mechanism ~~supporting~~that supports learning and memory functions, was shown to be severely impaired in old Tg2576 mice [51]. In the PDAPP mouse model, abnormal neurotransmission in hippocampal circuits can be detected before the formation of extracellular deposits of A $\beta$  peptides [104]. A $\beta$  peptide oligomers rapidly and significantly block LTP [320]. PS1 mutation alone can also induce anomalies ~~of~~in synaptic transmission that are similar to those observed after the application of A $\beta$ 42 peptide and are probably related to a decrease in the number of synapses [187] rather than to a modulation of their function [246].

In conclusion, the data ~~of~~in the literature suggest that synaptic alterations could be directly correlated with a high concentration of A $\beta$ 42, the amyloid conformation ~~adding~~ probably adding some supplementary detrimental constraints on the dendrites. They also suggest that electrophysiological alterations may be present in the absence of structural changes and that A $\beta$  oligomers are responsible for these changes.

*Synapses and connections* It has been known for a long time that neurites ~~making up~~comprising the corona of the senile plaque contain synapses. The origin of the axons that contribute to this ~~“innervation”~~“innervation” of the plaque is unknown except in rare circumstances (for instance, the axons in the superficial part of the molecular layer of the dentate gyrus come from the entorhinal cortex; they probably heavily contribute to the ~~plaques~~plaque’s innervation in that region). It has been possible to track ~~cortico-cortical~~corticocortical connections with an anterograde tracer in APPxPS1 mice and to show that some of them came into contact with the plaque core, while thalamic connections for instance avoided the plaque by following a curvy trajectory [74,75]. Entorhinal axons form dystrophic boutons in contact with A $\beta$  deposits located in the entorhinal projection area of the dentate gyrus [241]; aberrant boutons were found associated with amyloid in ectopic locations within the hippocampus, the thalamus, white matter tracts, as well as surrounding vascular amyloid [241]. These data show the presence of profound changes in neuronal connections that had been underestimated and probably contribute to dementia.

#### *Pathology of neurites and axonopathy*

The amyloid deposits induce massive changes in the neurites that surround them (the corona of the plaque). They are ~~labelled~~labeled by ~~anti-neurofilament~~antineurofilament and anti-APP antibodies (PDAPP mouse line, 10–12 months of age) [207]. The tau immunoreactivity of the corona neurites has attracted much ~~attention~~attention, since it may constitute the missing link between A $\beta$  and tau pathology. Phosphorylated tau and ubiquitin epitopes ~~appear~~ generally ~~late~~,appear late on, after 14 months of age in the PDAPP line [207]. No paired helical filaments (PHF) have ever been identified at electron microscopy [207] (with the noticeable exception of Kurt et al. [176]). The dystrophic ~~neurites~~,neurites in the Tg2576 ~~mouse~~,mouse are enriched in ~~GSK3 $\beta$~~ GSK3 $\beta$ , suggesting that this kinase is principally



responsible for tau phosphorylation [303]. In a APP<sub>Swe/L</sub> ~~×PS1 model~~ × PS1 model, most Aβ peptide deposits are surrounded by a high number of degenerating neurites containing APP, ubiquitin, and ~~manganese-dependent~~ manganese-dependent superoxide dismutase. Mitochondrial markers (cytochrome c, cytochrome oxidase 1, and Bax) are also in these degenerating neurites. Phosphorylated tau immunoreactivity appears late and develops at a slow pace [25].

The accumulation of neurofilament, APP, tau and ubiquitin epitopes is associated with morphological changes of the neurites. The amyloid core of the ~~plaques,~~ plaques in PDAPP mice crossed with mice overexpressing yellow fluorescent protein (YFP) in a subset of ~~neurons,~~ neurons is surrounded by markedly enlarged YFP-labeled axonal and dendritic varicosities [36]. The geometry of the neurites in or near the amyloid core is modified [190]. The presence of abnormal axonal varicosities near fibrillar deposits has also been observed in vivo by transcranial two-photon imaging [304] (Tg2576). An alteration of axonal transport has been considered ~~asto~~ be the possible cause of these changes: spheroids and myelin ovoids, axonal accumulation of APP, neurofilament and ubiquitin are observed in the white matter of the spinal cord [337] in the ~~APP×PS1~~ APP × PS1 and ~~APP×PS1—Ki~~ APP × PS1—Ki lines developed by Sanofi-Aventis [26,336,337]. Anterograde tracing of cortical connections has also revealed abnormal boutons in contact with the amyloid core [75,241]. The tracing of connections by DiI, a lipophilic carbocyanine dye, has been used by ~~Capetillo-Zarate~~ Capetillo-Zarate et al. [45]. They found, in the APP23 mouse line, a selective vulnerability of commissural neurons.

#### *Pathology of the cholinergic and other ~~neurotransmitters system~~ neurotransmitter systems*

Cell loss affecting basal forebrain cholinergic areas (observed in people with AD [330],) has not been reported in transgenic mice ([125]; reviewed in [102]) except in the trisomy 21 model (trisomy 16 in the mouse) [141,265]. Dystrophic cholinergic neurites, ~~on the contrary,~~ in contrast, have been regularly observed in contact with congophilic plaques [38,200,292]. Several studies have demonstrated decreased cholinergic terminals in APP [103] or APP/PS1 [342] transgenic mice (see ~~however,~~ however, [81] for mixed results). The Tg2576 mouse shows a significant elevation in the density of cholinergic synapses in the frontal and parietal ~~eortices~~ cortices, but in the double transgenic ~~Tg2576 × PS1~~ Tg2576 × PS1<sub>M146L</sub>, the density of cholinergic synapses is significantly reduced in the frontal cortex. The size of these synapses is smaller than in ~~wild-type~~ wild-type animals in the frontal cortex and hippocampus [342]. A re-organization of cholinergic innervation (reduction of acetylcholinesterase-positive fibers in the subiculum; increased fiber density in CA1 and in the dentate gyrus) has also been mentioned [38]. Minor changes in acetylcholine release were measured by microdialysis [121]. Decreases in the enzymatic activity of the cholinergic, serotonergic and noradrenergic systems were noticed only in the more aggressive models such as the APP23 [311]. These data indicate that the changes in neurotransmission are, as far as ~~it is~~ presently known, limited in APP ~~tg~~ Tg mice, which ~~are,~~ therefore, are therefore poorly adapted to ~~test~~ testing therapeutics ~~aiming~~ aimed at improving neurotransmission in AD.

#### Alterations that are lacking in the APP transgenic mouse models

Despite the many similarities between the pathology of AD and of its Tg models, the APP Tg mouse is not a perfect replica of AD. The most striking difference is the absence of NFTs. Even if hyperphosphorylated tau has been detected with immunohistochemical methods, as we have seen, PHF ~~have,~~ has, to our knowledge, never been found. The link that has been postulated in the cascade hypothesis between the alteration of APP metabolism and tau accumulation has not been ~~reproduced~~ reproduced, and the reason ~~of~~ for this failure is still unknown. On the other hand, the large predominance of Aβ deposition on all other lesions in the Tg mice ~~gives~~ provides a new opportunity to

study the effect of ~~studying~~ A $\beta$  accumulation as if in isolation, ~~the effect of A $\beta$  accumulation~~, not mixed with tau pathology.

## Problems and questions

The transgenic animals, by allowing the exploration of uncharted territories, ~~have~~ revealed new pathogenic ~~possibilities which, for possibilities~~, although many of ~~them, these~~ cannot yet be proven in the human. There ~~are~~are, on the other ~~hands, hand~~, some discrepancies between the data obtained in the mice and in man, which remain unexplained. ~~We have collected in~~In this section ~~we discuss~~ the discrepancies and the open questions.

## Atrophy

The atrophy of the medial part of the temporal lobe, including the entorhinal cortex, hippocampus and ~~amygda-~~ ~~la~~amygdala, is probably one of the ~~best-established~~best-established signs of AD. Atrophy has also been detected in the main APP transgenic lines, but with an unexpected time course. Most of the studies that have evaluated brain atrophy in transgenic mice have been carried out in the PDAPP model [84,109,250,309,327]. These investigations reported a reduction in hippocampal volume and a severe atrophy or agenesis of fiber tracts (fornix and corpus callosum). The alterations are already observed in young animals (~~3 months~~)(three months) before the accumulation of A $\beta$  and show no further deterioration in older mice [84,109,250,309,327]. They have to be considered in parallel with the difficulties met ~~in finding~~when searching for a significant neuronal loss in Tg animals (see ~~later~~ the next section on ~~neuronal loss~~:"Neuronal loss"). Atrophy in Tg mice may therefore be the consequence of a developmental defect [124,202,] that could be amplified in strains with specific genetic backgrounds [202]. This observation ~~leaves open~~suggests the possibility that some functional alterations observed in Tg mice are related to developmental changes rather than to ~~the~~ accumulation of A $\beta$  peptide. Alternatively, the atrophy could be related to early alterations caused by the toxicity of A $\beta$  oligomers before the formation of plaques.

The ~~comparison~~comparison, by *in vivo* MRI, of APP/PS1 Tg mice (Double Thy1 APP751 ~~SL x HMGSL~~ x HMG PS1 M146L developed by Sanofi-Aventis [26]) ~~and of~~with plaque-free PS1 Tg mice did not reveal atrophy in young APP/PS1 animals. Hippocampal volumes are not affected by APP overexpression, regardless of age. However, an age-related atrophy occurs in APP/PS1 mice, involving posterior brain regions, including the midbrain and the internal capsule, the corpus callosum and the fornix. The pattern of atrophy, ~~that~~which involves white matter and largely spares the isocortex and hippocampus, is different from that reported in AD patients [76].

## Neuronal loss

Contrarily to the popular belief that neuronal loss is the essence of Alzheimer pathology, neuronal loss is particularly difficult to assess and opposite views have been expressed concerning its course and severity in AD (see for ~~in-~~ ~~stance:~~instance [108,254]). Roughly speaking, two ~~contrasted~~contrasting opinions have been ~~expressed:~~for expressed. For some, the neurotoxicity of A $\beta$  peptide is directly responsible for the neuronal death [348]. Numerous cellular models have indeed shown, ~~in vitro,~~ ~~vitro~~, the toxicity of the peptide (or even of part of the peptide) and ~~have~~ quantified the cell death that it induces. However, it is not yet clear how these results obtained outside ~~a~~ living tissue ~~may~~can be transposed to the whole brain. In the human, for instance, large diffuse deposits are commonly seen in intellectually normal aging persons and in the absence of overt neuronal death; they may surround ~~normal-look-~~ ~~ing~~normal-looking neurones [73,80]. On the other hand, the neurofibrillary pathology has often been incriminated as the direct cause of ~~the~~ neuronal death. The ~~"ghost tangles"~~ i.e. "ghost tangles" (i.e., tangles left in the extracellular space after the death of the neurons that contained ~~them, them~~) are a direct proof of the neuronal death caused ~~by~~by

or at least associated ~~with~~ with the NFTs [33]. Finally, other ~~still~~ as yet unknown mechanisms have been incriminated [108].

~~Results~~ Conflicting results have also been ~~conflicting in~~ obtained for the transgenic ~~mice~~ mice, and ~~even~~ a paradoxical increase in the number of neurons has ~~even~~ been noticed in young animals of the Tg23 mouse line [29]. As a general rule, the neuronal loss has been mild or absent in singly transgenic ~~lines~~ lines: no significant neuronal loss has been found in the isocortex or hippocampus of PDAPP mice [146] except in the immediate vicinity of amyloid focal deposits [307] and in the Tg2576 mice [145]. Mild neuronal loss was described for instance in the APP23 mouse line [44] ~~or~~ and in the CA3 sector of ~~the~~ PDAPP mice [136]. By contrast, the neuronal loss was found to be moderate or severe in doubly transgenic mice (~~Tg2576 × PS1-M146L~~) (Tg2576 × PS1-M146L [307]; Swedish ~~&~~ and London mutations ~~×~~ PS1 × PS1 (M146L) [271]; Swedish ~~&~~ and London mutations ~~×~~ × knock in PS1 (M146L) [48]; ~~5 × FAD~~ 5 × FAD [231]). In the majority of the lines, the neuronal loss involves the hippocampus (with a few ~~exception~~ (Cingulate ~~te~~ exceptions—cingulate cortex: PSAPP mice [307]; layer V of the isocortex [231]). The cause of the neuronal loss has been discussed: A $\beta$ 42 peptide at high concentration [231], amyloid A $\beta$  deposits [307]; intracellular A $\beta$  [48]. There is, however, some consensus ~~to consider~~ that the possible toxic effect of A $\beta$  peptide on the neurons is not direct, since the loss is not correlated with the amyloid burden, may be absent in regions rich in A $\beta$  deposits and, ~~on the contrary~~, ~~may~~ in contrast, can be seen at ~~a~~ some distance from them [271].

#### *The nature of the precipitated amyloid peptide*

The different isoforms of A $\beta$  peptide are the main [260], ~~maybe~~ and possibly the only ~~constituent~~ [283], constituent of the core of the senile plaque observed in the human. These isoforms include ~~full-size~~ full-size A $\beta$  ~~peptide~~ peptides 42 and 40 as well as N-truncated molecules that could represent up to ~~60%~~ 60% of all the A $\beta$  species. The major truncated variants consist of A $\beta$  peptide starting at AA 2–5 and 8–10 [275]. ~~Post-translational~~ Post-translational modification leads to alteration of the A $\beta$  molecule: isomerization, racemization, pyroglutamyl formation, oxidation, and covalent linkage of A $\beta$  dimers [175]. As a consequence, the A $\beta$  peptide of the human senile plaque appears particularly difficult to ~~solubilise~~ solubilize.

A $\beta$  deposits observed in transgenic mice resemble those depicted in human patients, showing classical immunoreactivity with specific anti-A $\beta$  antibodies and also amyloid characteristics following histochemical stainings (green fluorescence with thioflavine-S and Congo red birefringence under polarized light). The deposits of A $\beta$  peptide in the APP Tg mice contain ~~A $\beta$ -40~~ A $\beta$ 40 and ~~A $\beta$ -42~~ A $\beta$ 42 as in the human [297], but ~~has~~ have different ~~physico-chemical~~ physicochemical characteristics. At variance with what is observed in the human, in the APP23 Tg mice [175], as in Tg2576 mice [159], the A $\beta$  peptide is fully soluble in buffers containing SDS. This is attributed to the lack of the post-translational modifications that are observed in man [175]. Quite intriguing is the weak affinity of the transgenic murine amyloid to the Pittsburgh compound-B (PIB) that is used in the human to visualize the senile plaques [167]. Changes in affinity might be caused by differences in the secondary structures of A $\beta$  peptides deposited in human and mice brain tissues.

#### *The topography of the A $\beta$ deposits*

The topography of the A $\beta$  deposits follows, in man, a stereotyped progression that has been formalized by Thal et al. [302] (isocortex, hippocampus, basal ganglia, brainstem, cerebellum). This progression is not replicated in the Tg mice, where A $\beta$  deposits often ~~mainly~~ affect ~~in priority~~ the hippocampus, and ~~where it~~ largely depends on the promoter that is used.

#### *Intracellular A $\beta$ peptide*

The abundance, the significance and even the presence of intraneuronal A $\beta$  peptide (IA $\beta$ ) in man are now discussed. ~~Difficult~~Since it is difficult to distinguish from lipofuscin, IA $\beta$  has probably been underestimated in human neuropathology. A technical factor altering the IR of A $\beta$  peptide may have contributed to this ~~underestimation~~~~underestimation~~: the use of heat enhances the visualisation of IA $\beta$ , but formic acid impedes it [70,71,238]. Formic acid is commonly used to enhance the IR of extracellular A $\beta$ . The use of antibodies directed toward the N- and C-termini of the peptide has demonstrated that ~~most~~ the IA $\beta$  is mainly made up of the 42 isoforms and is N-truncated (see for instance [113,325]), so it is possibly the cleavage product of  $\alpha$ - and  $\gamma$ -secretase. There is some controversy concerning the abundance of intracellular A $\beta$  peptide: Wegiel et al. detects it even in glia and at a young age. For them, it is unrelated to AD pathology, ~~being~~since it is observed in regions where A $\beta$  deposition does not occur [325]. ~~For others,~~ ~~on~~On the ~~contrary,~~other hand, for others, intraneuronal A $\beta$  ~~accumulation~~accumulation, which takes place within the multivesicular ~~bodies~~[bodies [294], ~~a~~] (a specialized form of ~~lysosomes,~~lysosomes) is an essential factor of the pathogenesis [18,113,178,294,334]. It has been seen in Down syndrome ~~patients,~~patients before the appearance of senile plaques [115,221]], and is said to be present in vulnerable regions before the development of full-blown pathology [113].

This point of view has been stimulated by the analysis of Tg mice. Large granules containing A $\beta$  peptide immunoreactivity ~~have, indeed,~~have indeed been seen within the cortical neurons of several transgenic ~~lines among~~ ~~which~~lines, such as Tg2576 mice [113,294], APP<sub>SL</sub>PS1<sub>M146L</sub> [186,335], APP<sub>SL</sub>PS1<sub>M146L</sub>KI [48] and ~~3xTg-AD~~3  $\times$  Tg-AD mouse [233,234]. In the transgenic models, A $\beta$  intraneuronal accumulation is easy to identify and much simpler to distinguish from lipofuscin than in man. The density of intraneuronal A $\beta$  peptide decreases while the density of extracellular A $\beta$  deposits increases [186,234,335]], suggesting that the secretion of intracellular A $\beta$  is responsible for its extracellular accumulation. The removal of extracellular A $\beta$  deposits (by immunotherapy) is shortly followed by the clearance of intraneuronal A $\beta$ , indicating that there is a dynamic balance between the two pools [234].

In conclusion, the frequency of intracellular A $\beta$  peptide accumulation and its temporal relationship with the extracellular deposits in transgenic mice raise new questions: does the intracellular accumulation also constitute a constant stage in the neuropathology of AD? Should the cascade hypothesis be changed accordingly [334]? Is it, ~~on the contrary,~~ ~~the consequence of~~ contrast, due to the overproduction of A $\beta$  peptide, observed only in a subset of AD (genetic cases)? Is its easy recognition in Tg animals the mere consequence of the artificial overexpression of APP? If the extracellular A $\beta$  ~~takes its origin~~originates in the intracellular pool, why ~~is doesn't~~ the extracellular pool ~~not~~ only ~~constituted~~consist of N-truncated species? No other example better illustrates the interplay between AD and its experimental models. The emphasis ~~put~~placed on intracellular A $\beta$  is clearly ~~the~~a consequence of the scrutiny of the transgenic mice. On the other hand, its importance in Tg models ~~lead~~has led to ~~re-assess~~a reassessment of its role in the human.

### *Kinetics of the change*

Multiphoton confocal microscopy, ~~that~~which does not induce the lesions caused by the high energy of the laser beam used in standard confocal microscopy, allows the examination of ~~a~~ living tissue. This technique has been applied to living transgenic animals, ~~allowing to visualize~~such that the cortex can be visualized through a window made in the skull. ~~Observation, during~~Observations made over periods of ~~months,~~has months have provided new insight into the kinetics of the A $\beta$  deposits in the parenchyma and in the vessel walls: ~~Focal~~focal amyloid deposits develop rapidly. They could be followed over periods of up to ~~5 months.~~five months. Most of them remain stable in size and shape. Only a small population of the deposits ~~grows~~grew or ~~shrinks~~shrunk in Tg2576 mice [59]. ~~Topical~~The topical application of anti-A $\beta$  antibodies cleared diffuse and focal deposits over a ~~3 to 8 day~~3–8-day period [14].

Intracortical injections of adeno-associated virus (AAV) containing the gene for enhanced GFP in TG2576 allowed ~~to visualize~~ some ~~neurons,~~neurons to be visualized, the processes of which could be followed ~~on~~over long distances.

Around ~~14%~~14% of all the dystrophic processes in contact with the amyloid core were dendritic. Neurites did not penetrate the dense amyloid cores but ~~curve~~curved around them. A severe deficit in spine density (~~-50%~~)(-50%) was noticed within a distance of 20  $\mu$ m from the plaque edge. A ~~decrement~~decrease (-25%) also occurred on dendrites not associated with plaques. Plaques and dendrites ~~remain~~remained stable over the weeks of observation [286]. In a further study ~~with~~using the same methodology, a small subset of spines (around ~~5%~~)(5%) was found to appear at ~~one hour~~one-hour intervals in the control groups, counterbalanced by a similar percentage of spines that ~~disappear~~,disappear. In the Tg2576 mice, spine elimination ~~increased~~increased, resulting in spine loss, especially in the near vicinity of the plaques [287]. In another experiment, the dystrophic neurites surrounding the amyloid core were visualized by their spontaneous fluorescence in the PDAPP/YFP model mentioned earlier, while the amyloid core was revealed by the in vivo fluorophore ~~methoxy-X04 that~~methoxy-X04, which has a high affinity for amyloid. Dystrophic neurites appeared stable over a ~~3-day~~three-day period. Antibodies applied at the surface of the brain partly cleared the A $\beta$  deposits but also significantly improved the neuritic dystrophy within ~~3-days~~three days [35]. In Tg2576 mice, methoxy-X04 reveals that the first vascular amyloid deposits ~~involves~~involve the leptomeningeal arteries as multifocal deposits of band-like A $\beta$ . New observations made at weekly intervals showed an increase in the number of amyloid bands and a widening of those already present. ~~With the~~Over time, the propagation of existing bands ~~took over~~overtook the initiation of new ones [255]. In conclusion, ~~the observation of the kinetics of the~~these lesion ~~in-~~dicateskinetics observations indicate that the amyloid deposits are relatively stable, and that the amyloid angiopathy progresses initially by initiating new foci of deposition and later by increasing their size. The study of the dystrophic neurites suggests that they are relatively inert, while a small population of spines is continuously modified by plastic changes. An increase in the number of disappearing spines that is not balanced by ~~an increase of a~~ similar ~~magn-~~tudeincrease in the number of new spines explains the loss of spines that is found in the Tg2576 mouse line.

### *Inflammation and gliosis*

The presence of microglia within the senile plaque and of astrocytes surrounding the amyloid core has been known for a long time and is mentioned in ~~the~~ classical ~~text books~~.textbooks. These glial cells have been shown to express numerous inflammatory cytokines (reviewed in [2]). The presence of microglia and of astrocytes around the focal A $\beta$  deposits has been abundantly documented in Tg mice. The first inflammatory changes are observed quite early, before any visible A $\beta$  deposition. They are associated with increased BACE activity [123]. However, the cytokines whose ~~expression is~~expressions are induced by A $\beta$  peptide, particularly the peptide in its fibrillar form, ~~are~~have been discussed and contradictory results have been published in the literature [20,209,217]. In the Tg2576 mouse line, for instance, IL-1 $\beta$  and TNF- $\alpha$  -immunopositive microglia as well as IL6 immunopositive astrocytes have been found in close contact with amyloid A $\beta$  deposits [20]; the authors conclude that these changes are similar to those seen in man. Mehlhorn et al., in the same mouse line, only found an overexpression of IL-1 $\beta$  in the reactive astrocytes that surrounded the amyloid ~~deposits~~deposits, and concluded that the local immune response in transgenic Tg2576 mouse brain was different to that observed in brains from AD patients [217]. The microglial cells present in the plaque are partly derived from the bone marrow, as demonstrated by grafting bone marrow from ~~mice expressing~~ enhanced green fluorescent ~~protein expressing mice~~.protein. Fluorescent microglia was detected around the amyloid ~~deposits~~,deposits when the graft had been ~~done~~performed before the onset of pathology; they were less abundant when the graft was done in ~~an~~ old animal [204]. The presence of activated microglial cells in contact with the A $\beta$  deposits has been explained in different ways: for Wegiel et al. [324,326], the microglial cell is the ~~“driving force”~~“driving force” responsible for the transformation of ~~non-fibrillar~~nonfibrillar A $\beta$  into ~~congophilic, amyloid~~congophilic amyloid deposits, while for others it is ~~associated with~~linked to the inflammation that is associated with the amyloid core [20,295]. The effects of inflammation have also been discussed and ~~apprehended~~captured through transgenic technology. It ~~is to~~should be ~~noticed~~noted that several experimental data have uncovered the positive role of ~~in-~~



~~flammation~~:inflammation. TGF- $\beta$ 1 overexpression promoted the clearance of parenchymal A $\beta$  by microglial cells but increased amyloid angiopathy [343]. The level of C3 complement factor was elevated in these mice. To inhibit C3, soluble complement receptor-related protein y, a complement ~~inhibitor~~inhibitor, was expressed with hAPP. The amyloid pathology was increased ~~2-two-~~ to ~~3-fold~~threefold, suggesting that the activation of the complement that took place in the Tg mice was useful [345]. The inhibition of C1q (the recognition component of the classical complement activation pathway) had an opposite (although less marked) effect. The absence of its gene in Tg2576 mice and in APP/PS1 mice did not modify the amount of A $\beta$  deposition and its amyloid transformation. However, it was associated with a lower level of glial activation around the A $\beta$  deposits and improved the loss of synaptophysin and of MAP2 immunoreactivity. The A $\beta$  deposits were reduced when double transgenic ~~APP<sup>swe</sup>/PS1~~APP<sup>swe</sup>/PS1 delta E9 mice were crossed with mice overexpressing IL-1  $\beta$  [277]. Injection of lipopolysaccharide ~~in~~into the hippocampus of APP/PS1 mice stimulated recruitment of microglia and reduced A $\beta$  burden [204]. It is also clear that passive or active immunotherapy, ~~with the common consequence of bringing~~which both bring anti-A $\beta$  antibodies ~~in~~into contact with the amyloid ~~deposits~~deposits, produced spectacular results in the PDAPP mouse [269] and indicated that inflammation was not necessarily detrimental.

However, the ~~benefices~~benefits of inflammation ~~have to~~must be ~~counterbalanced by~~contrasted with the deleterious effects ~~noticed~~observed after the overexpression of several inflammatory ~~proteins~~,proteins. These data ~~that~~ helped ~~advocating to~~advocate an anti-inflammatory strategy in AD:  $\alpha$ 1-anti-chymotrypsin, an acute-phase inflammatory protein, promoted amyloid pathology when ~~co-expressed~~coexpressed with hAPP in singly Tg mice [224,230]. ~~Co-expression~~Coexpression of ~~Cox2~~,Cox2, an enzyme implicated in inflammation and inhibited by a class of anti-inflammatory drugs, with APP<sub>swe</sub> and PS1<sub>A246E</sub> did not modify A $\beta$  pathology but induced an elevation in the number of phosphorylated retinoblastoma (pRb) tumor suppressor protein and active caspase-3 immunopositive neurons [346].

In conclusion, the presence of astrocytes and microglia around the amyloid core of the plaque is seen both in the human and in the Tg mice. The inflammation ~~is however~~is, however, less severe in the latter [272]. The immunological mechanisms involved, the cytokines that are secreted, and even the effect (beneficial or detrimental) of inflammation remain ~~discussed~~the source of much discussion, with contradictory results ~~published~~ in the literature. The spectacular effect of immunotherapy has, however, demonstrated that the microglia, when correctly stimulated, are able to clear the extracellular A $\beta$  ~~deposits and suggest~~deposits. This suggests that, on the whole, triggering an adequately oriented inflammation is a better strategy than attempting to silence it.

#### *Alteration of neurogenesis in hAPP transgenic mice*

Neurogenesis, restricted to the dentate gyrus and the subventricular zone in the ~~adult~~adult, has been found to be enhanced in Alzheimer disease [157]. Largely divergent results have been obtained in different mouse ~~lines~~,lines expressing either mutated APP alone or ~~mutated APP~~ with mutated PS1. A two-fold increase in BrdU incorporation in the PDAPP mice was initially described by Jin et al. [156]. Several authors found that the proliferation of the neural progenitors was reduced [86,88,122], with a parallel reduction ~~of~~in their survival [122], in connection with the amyloid deposits [88] or even before their appearance [86]. Zhang et al. found the effect on neurogenesis to be linked to the presence of a mutant PS1 gene [351]. Finally, the proliferation was found ~~to be~~ increased by Verret et ~~al.~~al., while the survival at ~~4-weeks~~four weeks of the newborn neurons was decreased in correlation with the A $\beta$  deposits [318]. The effect could also depend on the ApoE genotype (see later).

## Correlations between pathology and physiological alterations

Ideally, mimicking the lesions in a Tg mouse should induce clinical symptoms that are similar to those seen in man; as already mentioned, however, the signs depend largely on the topography of the changes. A L1C1 model could be S0 if the lesions, although a good replica of what is seen in ~~man are~~ man, do not ~~occurring~~ occur at the correct place (see ~~above~~ the “Signs, lesions, cause: the SLC reading ~~key~~ key” above). We will have the opportunity to study such situations in ~~the~~ tau mice. However, many attempts have been made to isolate specific signs that could be improved by the treatment and would allow a therapeutic screening.

### *Regulation of body weight, body temperature, ~~sleep. Increased~~ sleep; increased lethality*

Decreased thermoregulation and altered wake/sleep patterns have been described in PDAPP mice [139]. APP transgenic mice are occasionally reported to have reduced body weights and enhanced (premature) lethality [57,164,166,174,220]. These alterations depend on the genetic background and are still poorly understood: neurodevelopmental defects could be one of the factors; acute events (such as spontaneous epileptic seizures) might also play a role.

### *Behavioral changes in Tg mice*

Anomalous anxiety-related ~~behaviours~~ behaviors are occasionally noted in APP transgenic ~~mice either in the~~ mice, taking the form of either neophobia or, ~~on the contrary, of~~ in contrast, hypo-anxiety and reduced inhibition [85,101,182,237]. The anatomical correlates of these ~~behavioural~~ behavioral changes are unknown.

### *Neurological disorders*

Signs of neurological impairments have been described in both single APP and double APP/PS1 transgenic mice from different lines (~~i.e.~~ (i.e., PDAPP, Tg2576, APP23, TgCRND8, APP/PS1 lines). Motor dysfunction and difficulties in coordinating movements are shown by reduced grip strength and altered ~~behaviour~~ behavior on a beam or an accelerated rotating device (rotarod) [12,164,166,310]. The integrity of sensory functions ~~have~~ has not been fully documented in APP transgenic mice. Enhanced acoustic (startle) reflex in TgCRND8 mice may indicate ~~the~~ abnormal processing of auditory stimuli [213]. Impairments in visually-guided navigation (swimming to a cued location in a spatial environment) could reflect compromised visual abilities [166]. A number of studies indicate that APP transgenic mice are hyperactive [12,85,132,166,182,237], but ~~the~~ locomotor activity has been shown to be decreased in the APP23 model that develops severe cerebral amyloid angiopathy in addition to parenchymal A $\beta$  plaques [181,310].

### *Cognitive dysfunctions*

Based on the evidence of an amnesic syndrome and early medial temporal lobe pathology in AD patients, ~~behavioural~~ behavioral studies in APP transgenic mice have largely focused on learning abilities ~~in~~ for tasks relying on the integrity of the hippocampus. For reviews, see [13,83,129,169]. ~~Figs. 1,2,4)-(1)~~ **Water maze**

This test requires the animal to locate and swim towards an invisible platform in a water tank. During learning, the mouse is supposed to build a ~~“cognitive map”~~ “cognitive map” of the environment, a representation that enables the animal to locate the platform, regardless of where it enters the pool. Rodents with damage to the hippocampus are severely impaired. Almost all APP transgenic models have, to date, been screened in the water maze task. The majority of these studies indicate defects in navigation ~~behaviour~~ behavior. The transgenic mice reach the goal later and after having covered a longer distance; they may have difficulties remembering the location of the platform when



assessed during probe trials. These types of deficit, some of which ~~with~~ exhibit very early onset [57,310] have been observed in the PDAPP [53], Tg2576 [137,329], APP23 [163,181,310], TgCRND8 [57], and crossed APP/PS1 [198] models. It is important to keep in mind, however, that some reports ~~have~~ failed to demonstrate significant or robust learning and retention deficits in the water maze task [132,164,166] in both APP and APP/PS1 transgenic mice. The reasons for such discrepancies ~~remain to be understood~~ are still unclear. **2) (2) Spatial alternation**

The rodents have a natural propensity to alternate their visits from already-experienced locations to new ones. This ~~behaviour~~, behavior, that can either be analyzed spontaneously or conditioned by an explicit reinforced alternation rule, requires intact working memory abilities. Lesions of the hippocampus but also of the frontal cortex disrupt spatial alternation [180]. Spontaneous or reinforced spatial alternation has been extensively studied in the Tg2576 ~~model~~ model, with several reports indicating decreased performances ([51,65,131,137,182,237]; see ~~however~~ however, [166] for mixed results). The deficit is said to be detectable at an early age before overt A $\beta$  ~~deposition~~ deposition, and to increase with age. The deficits were questionable in female APP23 mice [181]. Additional reports illustrated reduced spatial alternation in double APPxPS1 transgenic mice ([131,132,333]; see ~~however~~ see, however, [197]). **3) (3) Object recognition**

Visual recognition memory is also sensitive to hippocampal dysfunction. Objects are shown to the mouse during an acquisition phase. Following a variable delay (from minutes to several ~~hours~~ hours), the mouse is ~~replaced~~ placed back in the test ~~arena with~~ arena, which now contains both familiar (previously shown) objects and new ones. The natural tendency of rodents is to explore the new objects (novelty attraction). Good performance in this test relies on the hippocampus, the perirhinal and entorhinal ~~cortices~~ cortices, and on their interconnection. Impaired recognition memory has been demonstrated in both APP [77] and APPxPS1 transgenic mice [135]. As mentioned ~~earlier~~ earlier, the ~~knocking-out~~ knocking-out of PS1 did not rescue the cognitive deficit in the APP mouse [77]. Conflicting results have been obtained concerning the object recognition task in the PDAPP mice (~~deficit~~-(deficit [85] which is possibly corrected by immunotherapy [82]; ~~absence of deficit~~-[53]). **4) (4) Sparing of “procedural memory” “procedural memory”**

The dichotomy between procedural memory (based on the acquisition of skills or of a sequence of procedures), which is relatively spared in AD, and declarative memory, which is affected at the initial stage, ~~can not~~ cannot be directly applied to animals. Some efforts have been made to test the ability to follow procedures in a stereotyped manner and to contrast it with the ability to build cognitive maps. The APP Tg mice are still able to apply at least some procedural strategies [85,139], especially when given ~~the choices~~ a choice between multiple strategies to solve problems [24,219], thus suggesting selective alterations of different memory systems in these mice (sparing of procedural ~~memory~~ memory, while relational ~~“declarative-like”~~ “declarative-like” memories are affected).

*Is extracellular accumulation of A $\beta$  peptide the cause of the deficit?*

An inverse correlation between cognitive deficit and amyloid accumulation has been reported in several studies involving singly transgenic APP mice (~~e.g.~~(e.g., [53,84]) and doubly transgenic mice (~~e.g.~~(e.g., [110,267]). The good correlation between the areas where A $\beta$  peptide accumulates and the type of cognitive deficit, and the efficiency of the immunotherapy ~~both on~~ in terms of the amyloid load and ~~on~~ the ~~behavioural~~ behavioral symptoms ~~are~~ also ~~in favour~~ ~~effavor~~ the hypothesis of a direct toxic effect of amyloid. However, some discrepancies are poorly compatible with this hypothesis: in some cases, the deficit is detectable without A $\beta$  accumulation [131,310]; ~~sometimes~~, sometimes it is observed after the A $\beta$  accumulation has taken place [135]; ~~sometimes~~ while at other times there is no deficit despite a severe amyloid load [23,24]. Cheng et al. [55], while working on mice bearing the Arctic mutation that alters the sequence of the A $\beta$  peptide and makes it more prone to precipitate in fibrillar form (without altering the ratio ~~A $\beta$ 42/~~ A $\beta$ 40) ~~demonstrate~~ A $\beta$ 42/A $\beta$ 40), demonstrated a striking dissociation between plaque formation and functional deficits. ARC6 mice had more plaques than J20 mice but essentially no behavioral deficits. Furthermore, ARC48 mice had markedly greater plaque loads than J20 mice but comparable or less severe functional deficits. This set of results,

from different mouse lines, suggests that it is not the fibrillar A $\beta$  peptide sequestered in the plaque that is responsible for the cognitive deficit, but rather some ~~other~~, other diffusible A $\beta$  species [329], or, as suggested more recently, intracellular A $\beta$  peptide.

#### *Pathogenicity of intracellular A $\beta$*

~~We have mentioned in~~In a ~~preceding~~previous section (~~Problems and question.Heading: (“Intracellular A $\beta$  peptide)”~~) we mentioned the controversy ~~concerning~~over the role of intracellular A $\beta$  peptide in the cascade of the pathogenetic events leading to neuronal dysfunction. Intracellular A $\beta$  peptide has also been considered ~~as to be~~ directly responsible for the clinical signs: in the ~~3 $\times$ Tg-AD~~3 $\times$ Tg-AD mouse, synaptic dysfunction is detected before the development of A $\beta$  extracellular deposits and of tangles, but in correlation with intracellular A $\beta$  accumulation [233]. The deficit in long-term memory ~~appeared~~ also ~~appeared to be~~ correlated with the accumulation of intracellular A $\beta$ . Immunotherapy rescued the deficit and was associated with ~~the~~ clearance of intracellular A $\beta$  that ~~re-appeared~~reappeared with the cognitive deficit when the effects of the immunotherapy ~~wane~~waned [22]. However, since the density of neurons containing intracellular A $\beta$  decreases with ~~age~~age, while cognitive deficits increase, intracellular A $\beta$  ~~can not~~cannot be the unique or even the ~~essential~~crucial factor responsible for the neuronal dysfunction.

#### *Pathogenicity of oligomers*

Since insoluble fibrillar A $\beta$  peptides do not diffuse and are thus unable to play a pathogenetic role, except by direct contiguity, other A $\beta$  compounds ~~able to~~that can be active at ~~asome~~ distance from the plaques have been looked for. As already alluded to, A $\beta$  peptides easily form dimers, trimers and, in ~~general~~general, oligomers that pre-exist ~~to in~~ in protofibrillar and aggregated A $\beta$  deposits. In recent years, oligomers have ~~been~~ repeatedly ~~been~~ found to play an important pathogenetic role, particularly ~~on in~~ in synapses (see ~~above~~)—~~for above~~)—for a review see [322]. In several studies the presence of oligomers is thought to be necessary to explain the experimental ~~observation: alteration~~observations. Alteration of the total amount of cerebral A $\beta$ , for instance, was not changed by A $\beta$  ~~immunization~~immunization, although cognitive dysfunction was improved in a TgCRND8 murine model of Alzheimer disease, suggesting that the antibodies acted on soluble A $\beta$  species [155]. Dodart et al. [82] injected a monoclonal m266 anti-A $\beta$  antibody ~~to into~~ PDAPP mice. The memory deficits were reversed in less than ~~24 hours~~24 h by a single intraperitoneal injection (which could not modify amyloid burden). The antibodies were supposed to act directly on the oligomers.

In the Tg2576 mouse line, deficits in spatial alternation (Y-maze) were noticed at ~~7 months~~seven months of age, before A $\beta$  deposits were seen in the brain, but at a time when the levels of soluble A $\beta$  40/42 were already elevated [237]. The memory ~~loss~~, loss detected at around ~~6 months~~six months coincided with the appearance of detergent-insoluble A $\beta$  ~~aggregates~~aggregates, but the inverse correlation between the aggregation of insoluble A $\beta$  and memory was lost when age was taken into account. The authors concluded that the insoluble A $\beta$  was a surrogate marker for small assemblies of A $\beta$  peptide that disrupted cognition and occurred as intermediates during the formation of aggregates [329]. In the same mouse line, dimeric A $\beta$  peptide was shown to accumulate in lipid rafts of cell membranes at ~~6 months~~six months of ~~age~~age, when the first memory alterations are observed. At that stage, A $\beta$  dimers are fully soluble in SDS [162]. Lesné et al. looked for an A $\beta$  species whose accumulation corresponded to the time course of the decline in spatial reference memory (appearing at ~~6 months~~six months and remaining stable for ~~7 to 8 months thereafter~~) also 7–8 months thereafter), again in the Tg2576 mouse line. They found that A $\beta$  peptide forms stable molecular assemblies that are preferentially made of trimers. The dodecamers (~~=4~~(four trimers) of molecular weight 56 (termed A $\beta$ \*56) were the best correlates of the memory deficit and the most likely ~~candidate~~candidates for the toxic species responsible for the memory deficit [192]. A direct ~~testing~~test of the hypothesis of the A $\beta$ -oligomers was

~~obtained~~ achieved by injecting ~~in the lateral ventricle of rats, having learned an alternation task,~~ the conditioned medium of a cell culture producing large amounts of A $\beta$  peptides and particularly of ~~oligomers~~ oligomers into the lateral ventricle of rats that had learned an alternation task. This injection caused a deficit in the learned task that was ~~“rapid,~~ rapid, potent and ~~transient”~~ transient” [60].

The transgenic models of neurofibrillary pathology

The first part of this review was centered on A $\beta$  pathology. Only dystrophic neurites of the corona of the plaque contain hyperphosphorylated tau epitopes; paired helical filaments are remarkably absent from these models. The neurofibrillary, tau part of the pathology is thus practically absent from the Tg mice that we have considered up to now.

#### *Normal and mutated tau transgene*

Tau is a phosphoprotein that belongs to the family of the ~~microtubule-associated protein;~~ microtubule-associated proteins; it binds to tubulin and facilitates tubule polymerization [61]. It has an axonal subcellular ~~localisation~~ localization in the normal adult brain. When phosphorylated it is detached from tubulin which ~~depolymerises—depolymerisation that favours~~ depolymerizes—this depolymerization favors axonal growth and plasticity. Six isoforms of the protein are known [107] ~~that,~~ which differ in the presence or absence of exons 2, 3, or 10. An alternative splicing of exon 10 produces either tau with four repetitive motives (4R tau) or tau with only 3 (3R tau) [107]. Hyperphosphorylated tau is the main constituent of NFT of AD, which contains both 3R and 4R tau. The NFTs of progressive supranuclear palsy and corticobasal degeneration are principally or exclusively made of 4R tau [276], while Pick body contains exclusively or preferentially 3R tau [39,40]. The presence of tau immunoreactivity in a ~~somato-dendritic~~ somatodendritic distribution in the absence of true NFT defines ~~“pre-tangle”~~ the “pretangle” [17]. A ~~somato-dendritic~~ somatodendritic distribution of tau is also found in argyrophilic grain disease. The subcellular distribution of tau (axonal or somatodendritic) depends on the distribution of its mRNA, not on signals included in the protein sequence [19]. No change in tau expression has been detected in AD, but intronic and exonic mutations of the tau gene are known to be the cause of ~~fronto-temporal~~ frontotemporal dementia linked with chromosome 17 (FTDP-17).

The physiology of tau protein is different in adult mice and adult humans. Mouse brain contains ~~exclusively~~ the 4R tau ~~isoforms;~~ isoforms exclusively, whereas levels of 3R and 4R are approximately equal in normal adult human brain. Although mouse and human tau sequences are similar, there are 14 amino acid differences in the N-terminal region [8].

The normal shortest 3R tau isoform (3R tau without N-terminal insert) has been introduced ~~in~~ into the mouse genome under the promoter of the murine 3-hydroxy-methyl-glutaryl CoA reductase gene [37]. Tau immunoreactivity was present in the ~~somato-dendritic~~ somatodendritic compartment. Several ~~epitopes;~~ epitopes known to be phosphorylated in ~~AD;~~ AD were also phosphorylated, but there were no NFTs. The shortest tau isoform was also expressed under a murine prion promoter [147]. Insoluble, hyperphosphorylated tau inclusions were present in cortical and brainstem neurons but were mostly abundant in spinal cord neurons. There were no paired helical filaments at electron microscopy. Lines expressing the longest ~~4-repeat~~ four-repeat tau isoform under the murine thy-1 promoter (ALZ7 line) [112] developed a peripheral and central axonopathy [247,288]. Dilated axons, spheroids, and pretangles were observed without true tangle formation.

Another approach consisted ~~in~~ of expressing human genomic ~~tau;~~ tau contained in P1-derived artificial chromosomes (PAC). In line 8c, a ~~PAC;~~ PAC containing all 14 exons, ~~exon 1;~~ exon-1, and more than 7 kb of ~~5'~~ the 5' flanking region, which includes the tau promoter, was overexpressed in mice. Tau was distributed in neurites and at synapses,

but was absent from cell bodies. There were no significant pathological ~~changes~~ changes, while axonal spheroids and somatodendritic ~~distribution~~ distributions were observed in mice overexpressing 4R cDNA [90]. Htau mice were obtained by crossing tau knock-out mice with 8c mice [8]. Neither tau knock-out mice nor 8c mice develop any evidence of tau pathology. Htau mice exclusively express the ~~6~~ six normal human tau isoforms (without murine tau), the level of ~~the~~ 3R isoforms being significantly higher than that of the 4R isoform [8]. NFTs and extensive cell death were seen in the htau ~~mice~~ mice, although they express lower ~~level~~ levels of human tau than the c8 mice [8]. This suggests that ~~wild-type~~ wild-type murine tau prevents the aggregation of overexpressed human tau. Cell death in htau mice does not seem to be directly caused by the NFTs but appears to be linked to reexpression of proteins involved in cell-cycle and DNA synthesis [7]. NFTs were observed at a young age in mouse lines in which the P301L mutation was introduced [111,196] or the V337M mutation [296]. ~~Non-apoptotic~~ Nonapoptotic cell death and tau filaments were observed in transgenic mice with the P301S mutation of tau protein [3]. The expression of human ~~4-repeat~~ four-repeat tau with G272V and P301S mutations under a Thy1.2-promoter induced neurofibrillary pathology in the brain with severe cognitive alteration and no sensorimotor deficit [270].

In conclusion, PHF and NFT are usually not observed when any form of wild-type human tau is ~~expressed~~ expressed, except in the model developed by Andorfer et al. [8] in which mouse tau gene is knocked-out. In almost all of the models where cDNA ~~wild-type~~ wild-type tau is expressed, the distribution of tau is somatodendritic; only the construction of Duff et al. [90] using a minigene preserves a normal subcellular distribution of tau. Overexpression of mutated tau regularly produces NFT.

#### *Interaction between tau and A $\beta$ accumulation*

The influence of A $\beta$  hyperproduction on the neurofibrillary pathology was studied in different ways: injection of amyloid A $\beta$ 42 fibrils into the brains of P301L mutant tau transgenic mice caused a fivefold increase in the numbers of NFTs in cell bodies within the ~~amygdala~~ amygdala, from where neurons project to the injection sites [111]. In P301L mutant tau mice crossed with APP Tg2576 transgenic mice, the amyloid deposits occurred at the same age as in the Tg2576 simple transgenic ~~progenitor~~ progenitor, but the neurofibrillary pathology was substantially enhanced in the limbic system and olfactory cortex, suggesting a synergy between the ~~2~~ two pathologies [195].

On the other hand, reducing endogenous tau ameliorates or even completely rescues amyloid beta-induced deficits (the hAPP Tau ~~+/-~~ -/- mice had better results on cognitive test than hAPP Tau ~~+/-~~ that, themselves, +/-, which, in turn, had better results ~~than~~ than hAPP Tau +/+ mice). The presence of tau protein was also necessary to produce experimental excitotoxic lesions produced by the GABAA receptor antagonist pentylentetrazole [256].

The triply transgenic tau model expressing 3R tau (without mutation), APP with the Swedish and the London mutation and PS1 with the M146L ~~mutation~~ mutation, did not develop true NFTs; however, the mutated tau transgene and ~~hyperphosphorylated~~ hyperphosphorylated tau epitopes were found in the neuritic component of the plaque [32].

Oddo et al., instead of crossing single transgenic mice, ~~injected~~ simultaneously injected a P301L mutant tau transgene and an APP transgene bearing the Swedish mutation, both under a Thy 1.2 murine promoter, into single-cell embryos from mutant homozygous PS1<sub>M146V</sub> knock-in mice. The ~~2~~ two transgenes appeared to ~~co-integrate~~ integrate at the same locus. These triple transgenic mice (~~=3xTg-AD~~ = 3xTg-AD mice) finally bear a mutated ~~knocked-in~~ PS1 ~~gene knocked-in~~ gene, as well as a mutated APP and a mutated tau gene. At the first stage, A $\beta$  peptide accumulates intracellularly. ~~Secondarily~~ A $\beta$  then precipitates in the extracellular space. Intracellular tau accumulation is finally observed. As in the human, A $\beta$  accumulation is first seen in the isocortex, while tau pathology first appears in the limbic system [233]. The electrophysiological alterations (most noticeably, the deficit in LTP) are seen before extracellular accumulation of A $\beta$  peptide at a time when intracellular accumulation of A $\beta$  is already seen. Moreover, ~~the~~ injection of antibodies directed against A $\beta$  peptide first cleans the extracellular deposits before inducing

the disappearance of intracellular accumulation [234]. Normalization of the electrophysiological alterations is correlated with the disappearance of intracellular A $\beta$  peptide [233]. Increased tau levels and hyperphosphorylation has no effect on the onset and progression of A $\beta$  pathology [232]. However, the cognitive deficit ~~appears~~ does not only appear to be linked ~~not only~~ with A $\beta$  peptide; soluble tau species are also reduced after active and passive immunization and could be involved in the cognitive improvement caused by immunotherapy [235].

What is the physiological relevance of a triple transgenic mouse to explain sporadic AD or even familial AD (~~FAD~~)(FAD), which has never been found ~~to be~~ associated with a tau gene mutation? It is clear that no human disease is provoked by a triple mutation on the PS1, APP and tau genes. The model can therefore not be considered ~~as describing~~ to describe the cause of AD, and particularly of sporadic AD (C0). However, ~~it integrates~~ for the first time ~~it integrates~~ all of the lesions that have been described in the human (L1) in a topography that, in several ways, resembles the distribution of the lesions seen in man (S1). This model may therefore be considered, in our view, ~~as belonging~~ to belong to the SILIC0 type. It is probably too early to draw from this model the conclusion that A $\beta$  peptide deposition should precede tau pathology (it does in the model; ~~this~~ does not warrant that it occurs in this way in the human). In the same way, the conclusion that intracellular A $\beta$  is crucial ~~in the~~ to human pathogenesis because intracellular A $\beta$  is the best correlate of the electrophysiological signs in this triple transgenic model ~~can not~~ cannot be drawn, in our view, without a further and careful analysis of intracellular A $\beta$  in man.

#### *Persistence of the pathology in conditional KO mice*

To ~~analyse~~ analyze the mechanism of progression of the NFT, mice expressing a repressible human tau variant (rTg4510) were generated. The responder transgene consisted of a tetracycline operon-responsive element placed upstream of a cDNA encoding human tau with four microtubule binding repeats (4R tau) and the P301L mutation. Doxycycline, when introduced ~~in~~ into the food and water, suppresses transgene expression. Before doxycycline administration, the mice developed progressive age-related NFTs, neuronal loss, and behavioral impairments; when the expression of human tau was repressed, the cognitive deficit recovered and the neuronal loss remained stable but the number of NFTs continued to increase. This observation suggested that, not unlike what was observed in A $\beta$  pathology, the toxic effect of tau was not linked to the visible lesions (~~the~~ (i.e., NFTs) but to another tau species, the production of which was prevented by the repression of the tau gene [266]. These tau assemblies appear to be, just as in A $\beta$  pathology, multimers [21]. The toxic tau multimers of 140 and 170 kDa probably contain ~~full-length~~ full-length tau [21]. The progression of NFT despite the silencing of the mutated tau gene could indicate that NFTs, once present in the human brain, will progress even if a putative treatment is ~~active on~~ targeted at their cause.

#### *Modulation of APP transgene*

The effects of overexpressing or knocking out various known or supposed modulators of A $\beta$  secretion have been studied in the literature.

#### *Modulation of A $\beta$ secretion by APOE*

Apolipoprotein E is a protein involved in cholesterol transport. Its main receptor, the ~~low-density~~ low-density lipoprotein receptor-related protein (LRP), is widely expressed in the central nervous system. Moreover, ApoE [229,305,306] and LRP [10] ~~appears~~ appear to be bound with A $\beta$  in a large subset of senile plaques. Much was expected of ~~studies using~~ Tg mice to elucidate the role of apolipoprotein E (~~ApoE~~)(ApoE); the risk of developing AD is indeed increased in people bearing the epsilon 4 allele [291]. Actually, the expression of the various isoforms of human ApoE



in Tg mice and the knock-out of the ApoE gene in the mouse brought conflicting results and somehow increased the complexity of the problem.

### *Effects on A $\beta$ deposition*

A comparative study of the time ~~course~~courses of A $\beta$ 42, A $\beta$ 40, and ApoE deposition in relation to astrogliosis in Tg2576 suggested that A $\beta$ 42 preceded ApoE in the plaque, followed by ~~A $\beta$ 40~~A $\beta$ 40, which occupied the ~~center~~center of the deposit in later stages. Moreover, the presence of ApoE was correlated with the astrogliosis [297]. The A $\beta$  deposits were compared in *heterozygous* V717F APP Tg mice (APP<sub>V717F</sub><sup>+/-</sup>) with graded expression of the mouse ApoE gene. The mice carried no (ApoE ~~+/+~~;-/-), one (ApoE +/-) or two (ApoE +/+) alleles. Amyloid deposits as well as A $\beta$  immunoreactivity were lacking in the cortex in the absence of ApoE expression in animals aged 22 months. A $\beta$  deposition was ~~observed although~~observed—although at a lower level than in the ApoE +/+ ~~mice when~~mice—when only one allele (ApoE +/-) was present. ApoE immunoreactivity was found in all of the thioflavin S positive amyloid cores in the Tg mice with one or two ApoE alleles [15]. In a later study with *homozygous* V717F APP Tg mice (APP<sub>V717F</sub><sup>+/+</sup>) on an ApoE null background, it was found that the cortical and dentate gyrus deposition of A $\beta$  was dramatically ~~reduced~~reduced, but that the ~~density~~densities of the CA1 and CA3 diffuse deposits ~~was~~were increased even ~~if~~when there was no thioflavin S positive deposits [144]. The overexpression of ApoE4 in a hAPP mouse, ~~knock~~knocked out for ApoE, increases ~~10-fold~~ the number of focal, amyloid deposits ~~tenfold~~ in comparison with the ApoE3 mice [133]. Since the dystrophic neurites that are found in the ~~corona~~coronae of the plaques are only observed when the deposit is focal and amyloid, it is no wonder that no ~~“neuritic plaques”~~“neuritic plaques” are found in the ApoE ~~+/+~~-/- mice. The role of ApoE itself in the neuritic degeneration is discussed [133]. In *heterozygous* V717F APP Tg mice, A $\beta$  deposition was compared in mice expressing no ApoE, murine ApoE, or the various human ApoE isoforms (ApoE2, E3, and E4). As previously shown, ApoE was not necessary but it enhanced the formation of fibrillar A $\beta$ . Murine ApoE was the most efficient, then human ApoE4, E3 and E2. In other words, as in man, ApoE2 and ApoE3 delayed the formation of amyloid deposits when compared to murine ApoE and human ApoE4 [94]. In Tg mice bearing one allele of the Swedish (Sw) mutation (APP<sub>sw</sub><sup>+/-</sup>), the expression of the human ApoE4 (ApoE4<sup>+/-</sup>) (under the human transferrin promoter) accelerated A $\beta$  deposition and amyloid formation [47]. ~~But~~However, in another study, the overexpression of human ApoE4 under a murine prion protein promoter (responsible for ~~a~~ neuronal and glial expression) did not modify the amount and progression of A $\beta$  deposition in Tg mice expressing human APP<sub>sw</sub> or APP<sub>sw</sub> and PS1 with the deletion of exon 9 [193]. Van Dooren et al. compared the effects of expressing human ApoE4 in neurons (thy1 gene promoter) or in glia (GFAP gene promoter) of hAPP V717I singly transgenic and ~~APP-V717I xPS1A246E~~APP-V717I  $\times$  PS1A246E doubly transgenic mice (~~thy1~~(thy1 gene promoter for both transgenes). All of the mice were female and hemizygous for the transgene. The thy1 gene promoter construct is practically ~~not expressed~~unexpressed in the thalamus. The presence of the human ApoE4 allele had a differential effect on cortex and thalamus, ~~that~~which also depended on its ~~of production,~~production, neuronal(neuronal or ~~glial~~glial): in the cortex, neuronal ApoE4 increased the number of diffuse deposits of A $\beta$ , while in the thalamus, the density of both diffuse and focal deposits ~~was~~ increased with neuronal ~~as~~and with glial ApoE. Neuronal ApoE promoted cortical amyloid ~~angiopathy~~angiopathy, while both neuronal and glial ApoE had a similar effect on the thalamus. ApoE did not influence APP processing and was not associated with tau hyperphosphorylation (probably because the ApoE transgene was hemizygous) [314]. Since ~~in these constructs,~~ APP was not produced in the ~~thalamus,~~thalamus in these constructs, the accumulation of diffuse or focal A $\beta$  in this topography was related to its migration.

### *Effects on tau*

ApoE could have more widespread effects than suspected. Neuronal but not glial expression of ApoE4 resulted in hyperphosphorylation of protein tau and caused prominent axonopathy by ~~disruption of~~ disrupting axonal transport [299,300]. In various transgenic lines in which human ApoE3 or ApoE4 was expressed under a GFAP or a neuron-specific enolase (NSE) promoter, C-terminal fragments of ApoE4 (and to a lesser degree of ApoE3) accumulated, and tau protein appeared to be hyperphosphorylated only in the NSE-ApoE Tg mice [34].

### *Effects on synapses*

Buttini et al. found in hAPP mice that synaptophysin-immunoreactive presynaptic terminals, choline acetyltransferase (ChAT) activity, and ChAT-positive fibers were reduced in old apoE-deficient transgenic mice expressing human APP. This effect was prevented by the expression of the ApoE3 allele [41].

### *Conclusions*

The effect of ApoE on A $\beta$  metabolism and deposition is still controversial. The presence of murine or human ApoE does not directly modify the metabolism of APP, but increases the number of focal deposits, the number of their surrounding dystrophic neurites, and the level of vascular angiopathy. It could also be involved in the transport of A $\beta$ , since lesions are seen in the thalamus under conditions in which A $\beta$  is not produced by the thalamic neurons. The effects on the phosphorylation of tau are intriguing: they could ~~be provide~~ provide a link between A $\beta$  and tau alterations; alternatively, as tau hyperphosphorylation is only found when the neuronal expression of ApoE is high, ~~it they~~ they could be related to side effects of the transgenesis. The importance of ApoE ~~for to~~ to the trophicity of some synapses appears to be more firmly ~~established~~ established, since ~~they are it is~~ it is revealed by knocking out the murine gene. Strangely enough, whereas ApoE is known to be mainly produced by glia, most of the effects are found with a neuronal expression [9], and this should prompt a re-evaluation of neuronal ApoE in human pathology.

*Modulation of A $\beta$  deposition by other proteins involved in cholesterol ~~metabolism~~: metabolism: liver X receptor, LRP and ABCA1* Besides the essential role of ApoE in A $\beta$  deposition, a number of data ~~suggests~~ suggest a link between cholesterol metabolism and AD pathology. In APP Tg mice (PSAPP ~~line = TG2576 x PS1~~ line = TG2576 x PS1<sub>M146V</sub>), dietary cholesterol seems to accelerate A $\beta$  ~~deposition~~ deposition, whereas cholesterol-lowering drugs lower it [252,253]. Inhibition of acyl-coenzyme A cholesterol acyltransferase (ACAT), an enzyme that controls the equilibrium between free cholesterol and cholesteryl ~~esters~~ esters, was shown to reduce amyloid pathology [143].

The liver X receptor (LXR) regulates cholesterol metabolism and also plays a role in inflammation: it ~~in-~~ ~~hibits~~ inhibits the expression of genes involved in inflammation but promotes the phagocytosis of A $\beta$  by microglia. Deletion of either LXR $\alpha$  or LXR $\beta$  in APP<sub>swE</sub>/PS1<sub>deltaE9</sub> transgenic mice resulted in increased amyloid plaque load [349].

LRP is an endocytic cell-surface receptor that is abundant in neurons (cell body and dendrites). It allows the internalization of several ~~ligands, among which~~ ligands such as apoE, APP (with the Kunitz inhibitor) and  $\alpha$ 2-macroglobulin. LRP ~~knock-out~~ knock-out mice are not viable. van Uden et al. used mice deficient in receptor-associated protein (RAP) to reduce ~~by 80%~~ the level of LRP. LRP by 80%. They were crossed with the hAPP line J9. The amount of amyloid deposits was doubled on the RAP ~~+/+~~ background, while APP processing was not altered, suggesting ~~that, indeed, that~~ LRP ~~helped~~ does indeed help to clear A $\beta$ 42 [316]. On the other hand, overexpression of a functional mini LRP receptor (LRP2) in PDAPP mice produced a decrease in cerebral ApoE, a moderate but significant increase in insoluble, detergent soluble (probably membrane-bound) A $\beta$ 42, and a decrease in total A $\beta$  in the CSF. The decrease in the ApoE level is explained by an accelerated internalization and degradation of ApoE when LRP is overexpressed. The effect on A $\beta$ 42 is abolished in ~~ApoE +/+~~ ApoE ~~-/-~~ mice, suggesting that it is mediated



through the binding of A $\beta$ 42 to ApoE. In cell ~~culture~~ culture, the cells overexpressing LRP2 clear the A $\beta$ 42 present in the culture medium more rapidly [350].

ABCA1 (ATP-binding cassette transporter A1) is a major regulator of cholesterol efflux and ~~high-density~~ high-density lipoprotein (HDL) metabolism. The mutation of ABCA1 in the human causes severe ~~hypercholesterolemia~~, hypercholesterolemia and marked ~~deficit~~ deficits of ~~high-density~~ high-density lipoprotein (HDL) and of apoA-I. The level of ApoE is low in the ~~brain~~ brains of these patients. In APP23 Tg mice ~~knock-out~~ knocked out for ABCA1, the density of A $\beta$  and Congo red positive deposits is increased. The amyloid angiopathy is more severe and associated with ~~micro-haemorrhages~~. microhemorrhages. The level of soluble ApoE is decreased in the brain [171].

*Modulation of A $\beta$  secretion by  $\alpha$ -synuclein* Lewy and AD pathologies are often associated in the human and could have a synergistic effect. On the other hand, some rare cases of familial Parkinson disease are linked to several mutations on the  $\alpha$ -synuclein gene.  ~~$\alpha$ -synuclein-positive~~  $\alpha$ -Synuclein-positive neurites have been mentioned in the aged TG2576 (APP<sup>swE</sup>) transgenic line [347]. Such a pathology in a mouse line without any known alteration of  $\alpha$ -synuclein already hints ~~toward~~at cooperation between amyloid and Lewy pathology. The human wild-type or mutated (A53T)  $\alpha$ -synuclein gene has been expressed in mice under the control of the mouse Thy1 regulatory sequence [312]. Similar pathological changes were observed in the two mouse lines. The protein accumulated in the neurons and caused their degeneration. ~~But~~ However, for unknown reasons, the pathology involved unexpected areas: brainstem neurons and motor neurons of the spinal cord appeared particularly vulnerable. There was no expression of the transgenes in the substantia nigra pars compacta. In other mouse lines in which the wild-type or the mutated  $\alpha$ -synuclein gene was driven by the promoter of the tyrosine-hydroxylase [210]; no degeneration was observed in the substantia nigra despite a high level of expression. Overexpression of ~~wild-type~~ wild-type and mutated  $\alpha$ -synuclein in cultures of dopaminergic neurons, however, caused significant cell death. Cytoplasmic inclusions were observed only in the cultures where the mutant gene had been transfected.

Accumulation of  $\alpha$ -synuclein occurred earlier in ~~doubly—hAPP~~ doubly—hAPP (line J9) and ~~wild-type  $\alpha$ -synuclein—bigenic~~ wild-type  $\alpha$ -synuclein—bigenic mice. Some inclusions appeared fibrillar in the doubly transgenic animals, whereas they were always amorphous in the singly transgenic animals [206].

In conclusion, the effects of  $\alpha$ -synuclein remain ~~still~~ controversial: several reports indicate that even the wild-type form of the human protein may induce pathological changes. It ~~is, however,~~ is however surprising that, ~~contrarily~~ in contrast to what is observed in the human, the dopaminergic system appears resistant. Although still badly explained,  $\alpha$ -synuclein and APP seem to interact in the transgenic lines just as they do in the human.

*Modulation of the pathology by other proteins* Numerous doubly or ~~triple~~ triply transgenic lines (only some listed here) have been generated to elucidate the influence of a candidate protein on the secretion of A $\beta$  peptide or on the pathology that it generates.

#### *Transthyretin:*

Transthyretin (TTR) is a serum protein that precipitates in autosomal dominant familial amyloidotic polyneuropathy, in familial amyloidotic ~~cardiomyopathy~~ cardiomyopathy, and in sporadic senile systemic amyloidosis. It is also said to complex A $\beta$  peptide that is physiologically present in the CSF of controls and of patients and could prevent amyloid formation [273]. Mouse strains transgenic for either wild-type or mutant (TTR L55P) human TTR genes have been produced and develop TTR deposits in heart and kidney, only some ~~being of which are~~ congophilic. Hemizygous deletion of its gene ~~favours~~ favors A $\beta$  deposition in APP<sub>swE</sub>/PS1<sub>deltaE9</sub> mice [58].

#### *Oxidative damage*

The homozygous deletion of the superoxide dismutase 2 (SOD2), a mitochondrial enzyme implicated in the protection against oxidative damage, worsened the cognitive deficit and decreased the ~~microtubule-associated mi-~~

crotubule-associated protein 2 (MAP2) immunoreactivity, a sign of dendritic loss. Paradoxically, it lowered the density of  $A\beta$  deposits but increased amyloid angiopathy [93].

#### *Fyn*

Fyn, a tyrosine-kinase that is altered in AD brains, is located in the postsynaptic density of glutamatergic neurons. It could be involved in the signal transduction responsible for the toxic effect of  $A\beta$  on synapses. When overexpressed in hAPP mice lines J9 and J20, it induced impaired spatial memory retention and altered emotional ~~behaviour~~-behavior. It also caused other changes in the expression of ~~proteins~~proteins, such as Fos and calbindin [56].

#### *Modulation of the pathology by activity*

The effects of environmental enrichment on  $A\beta$  deposition are contradictory. It was initially found to improve cognitive function but to exacerbate amyloid plaque formation in APP<sup>swe</sup>/PS1<sup>dE9</sup> mice [150,151]. In a later ~~study~~study, increasing cognitive, social, or physical activities protected the Tg mice from the cognitive impairment without affecting amyloid deposition [11]. Physical activity (running wheel: [1]) as well as an enriched environment [5] was found to reduce  $A\beta$  ~~level~~levels in the TgCRND8 line, while another study did not find any significant effect on  $A\beta$  deposition in the APP-23 mice [339]. In ~~still~~yet another study involving doubly transgenic mice ~~TG2576 x PS1M671L~~, a “complete”TG2576 × PS1M671L, “complete” environmental enrichment (~~i.e.~~(i.e., in terms of cognitive, social and physical activities) was shown to ~~reduce~~significantly reduce the amyloid load (~~-28%~~(-28% in hippocampus and -36 in entorhinal cortex). The contradictory results ~~of~~in the literature suggest that the ~~effect~~effects of environmental enrichment and physical activity are related to additional, badly controlled factors. Recently, it has been suggested that the ApoE allele could play a role, since environmental enrichment stimulated apoptosis when the human ApoE4 was expressed on a murine ApoE deficient ~~background and on the contrary~~background, while it stimulated neurogenesis in ApoE3 mice [194].

#### *Trauma*

Repetitive mild traumatic injury of the brain increased the deposition of  $A\beta$  peptide in the Tg2576 mouse model. Single brain trauma had no effect [308].

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## Conclusions

The transgenic technology has, for the first time, allowed the production of some of the lesions observed in human neurodegenerative diseases. Its success proves, a contrario, how weak ~~were~~ the other methods based on the use of destruction, toxic agents or ~~observation~~observations of naturally occurring animal ~~diseases~~diseases were.

We have repeatedly seen in this review that the conclusion that may be drawn from a model depends on the joined analysis of the transgenic line and of the human disease. The renewed analysis of the lesions in the animal enlightens our view on the human pathology; ignorance of the human pathology ~~will, no doubt,~~will undoubtedly lead to erroneous interpretation. This crossed examination implies a double ~~competence~~—incompetence—in both human and animal pathology. The neuropathologist is a key scientist in the exploration of these new territories.

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~~Fig. 1~~ Fig. 1a–b Connections of plaques. ~~a~~ **a** The anterograde tracer biotinylated dextran amine (~~BDA~~) (**BDA**) was injected ~~into~~ **into** the mediodorsal nucleus of the thalamus. The prefrontal cortex was examined after Congo red staining. The anterogradely labeled fibers are shown in brown (~~long arrow~~) (**long arrow**). The normal connections are present and avoid the plaque, whose core is stained by Congo red (~~small arrow~~) (**small arrow**). ~~b~~ **b** BDA was injected ~~into~~ **into** the posterior cingulate cortex. Labeled fibers are visible in the visual cortex (~~black~~) (**black**), which is normally connected with the posterior cingulate cortex. Several fibers (~~arrows~~) (**arrows**) come into contact with the amyloid deposit (~~brown~~) (**brown**; immunolabeled by a polyclonal anti-A $\beta$ 42 antibody) and appear dystrophic. ~~Bar = 10  $\mu$ m~~ **Bar = 10  $\mu$ m** for a and ~~b~~ **b**. This experiment suggests that only a subset of the cortical connections ~~“innervates”~~ **“innervates”** the plaque (~~Delatour et al., 2004~~) [75]

Fig. 2 Comparison of extracellular deposition and intracellular accumulation of A $\beta$  peptide in APPxPS1 Tg ~~Mice~~ **Mice**. Five illustrative mice, taken at 2, 5, 9, 11, and 15 months of age, were studied. Sections, 25  $\mu$ m in thickness, were immunostained with an anti-A $\beta$ <sub>8–17</sub> antibody (clone 6F/D3; Dako, Glostrup). The extracellular deposits of A $\beta$  peptide are plotted on the left side in ~~green~~ **green**; the intracellular granules of A $\beta$  peptide are shown in red on the right side. Intracellular A $\beta$  is visible ~~as early as 2 months~~ **after just two months**, before the appearance of extracellular deposits. The density of intracellular A $\beta$  decreases with the increase in the density of extracellular deposits of A $\beta$  peptide. Scale ~~bar = 1 mm~~ **bar = 1 mm**. Modified from (~~Langui et al., 2004~~) [186]