



ALZHEIMER'S DISEASE

What can we hope for?

There has never been so much discussion before about this neurodegenerative disease that causes a progressive loss of memory and mental faculties. Indeed, because the number of patients is increasing, Alzheimer's disease has now become a public health issue.

Alzheimer's disease, which is an actual scourge, **will be one of the key topics of the 19th 2009 World Congress of Gerontology and Geriatrics**, held in Paris under the auspices of the IAGG (International Association of Gerontology and Geriatrics). Although much progress has been achieved in understanding the disease, prognosis remains very pessimistic. Symptoms can be slowed down, but the disease cannot be cured.

Professor Françoise Forette, geriatrician and Director of the *Fondation Nationale de Gérontologie*, reviews the current situation concerning this disease, its incidence and the latest advances in research.

Alzheimer's disease: how is it defined?

There is no such thing as "senile dementia", but a variety of causes for intellectual deterioration. Schematically, there are **vascular diseases and neurodegenerative diseases**, of which **Alzheimer's disease is the most common form, although the two processes are often intertwined**. However, the term "Alzheimer's disease and related disorders" is now used to describe various forms of dementia characterised by memory disorders associated with other signs and symptoms, such as executive function disorders, temporal and spatial disorientation, impaired language or judgement, etc.

There are two types of Alzheimer's disease: **familial disease** linked to well-known gene mutations, and **sporadic disease** which involves a variety of predisposing factors, including vascular factors and genetic characteristics such as apolipoprotein E4 which confer an increased risk for the disease.

Statistics concerning the disease

Alzheimer's disease accounts for 70% of dementia. **24 million people throughout the world are affected by dementia¹**. Global incidence is expected to increase fourfold by 2040, to affect 80 million people. **4.6 million new cases are diagnosed each year, i.e. one case every seven seconds. In France**, Alzheimer's disease is the leading cause of heavy dependence amongst the elderly and **affects 850,000 people**, i.e. 5% of those aged over 65 years and 15% over the age of 85. 225,000 new cases should be detected every year, but only one in two is diagnosed.

1. *Lancet*.2005; 366 :2112-7

With ageing of the population and the arrival of the baby-boomer generation, the number of people affected is expected to increase rapidly in France to reach two million in 2040 if no preventive treatment becomes available before then. **Women are three times more affected than men.**

The mechanisms of action of Alzheimer's disease

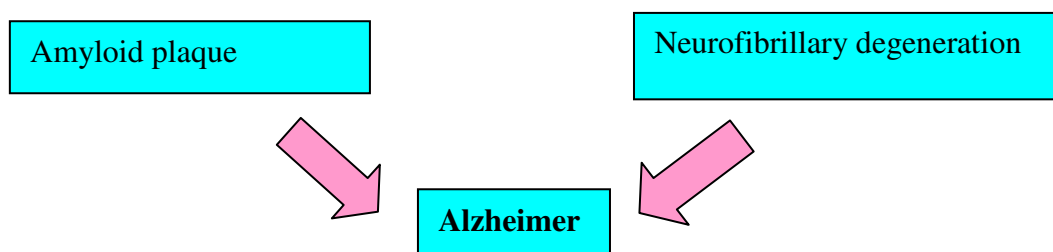
Alzheimer's disease is characterised by neuronal degeneration and death. Neurons in the hippocampus, the seat of memory, are the first to be affected. The disease then spreads gradually to other areas of the brain governing temporal and spatial orientation, the recognition of objects and people, language or reasoning.

Much progress has been achieved in understanding the mechanisms responsible for lesion cascade. **These include dysfunction of two proteins: the synthesis of abnormal quantities of amyloid beta protein 42 resulting from the abnormal division of APP (amyloid precursor protein) under the action of two enzymes: gamma- and beta-secretases, and tau protein.**

This dysfunction causes **two types of lesion:**

- the formation around neurons of amyloid plaques linked to the deposition of amyloid beta protein 42 surrounded by cell debris,
- and the formation of neurofibrillary degeneration due to hyperphosphorylation of the tau protein inside the neurons, causing cell death.

Although these mechanisms are now well understood, the way the shift from amyloid plaque to neurofibrillary degeneration occurs remains unexplained.



Neuronal dysfunction causes a **reduction in the release of neuromediators, mainly but not solely of acetylcholine. Current therapies are based on substituting these neurotransmitters. Three cholinergic agents and one NMDA receptor antagonist are now available.**

Major therapeutic challenges

The major challenge posed by Alzheimer's disease is the discovery of drugs that would be active on the disease process. **Most therapeutic strategies for the future are based on the amyloid theory**, i.e. the lesions are caused by the synthesis and deposition of this amyloid protein, which is over-produced in the familial form of the disease, or aggregated or deposited because of insufficient "clearance" in its sporadic form.

Research focuses on the following: the inhibition of gamma- and beta-secretases, prevention of the fibrillation of amyloid protein or the triggering of an immune reaction by a vaccine. Other, more recent, approaches have focused on the tau protein, attempting to prevent its inappropriate phosphorylation.

Newsflash on presentations during the congress

Two main topics are emerging from major presentations during the congress: **early diagnosis** using radiological and biological markers, and **new therapeutic approaches** to slow disease progression, whether these are drugs, psychological and medical and social management or preventive trials.

Early diagnosis and disease management

Major advances in neuropsychological tests and imaging (CT and MRI scans) now enable an effective diagnosis of Alzheimer's disease. However, **tools for early diagnosis have recently appeared**, including brain imaging and new biomarkers. As no preventive therapies are currently available, these methods cannot be considered as screening tools to be used in the general population, but in the years to come they will enable early identification of the disease with a view to start effective treatment at an early stage.

Presentation of the ADNI (Alzheimer's Disease Neuroimaging Initiative)

Keynote lecture - ALZHEIMER'S DISEASE NEUROIMAGING INITIATIVE (ADNI): A PROGRESS REPORT

Michael WEINER – University of California, Center for Imaging of Neurodegenerative Disease (San Francisco, USA)

Wednesday 9.45 a.m. – 10.15 a.m. - Amphitéâtre Bleu

Professor Weiner will provide a review on this very important initiative which is at the service of therapeutic and preventive studies and the aim of which is to identify predictive markers for Alzheimer's disease in normal subjects or in subjects suffering from MCI (Mild Cognitive Impairment). This ongoing study is conducted in 400 individuals with MCI, 200 individuals with Alzheimer's disease and 200 control subjects, who are being followed for three years using neuroradiological and biological markers and neuropsychological tests.

SB6 019 - UPDATE: DEVELOPMENT OF THERAPIES AND DIAGNOSTICS FOR THE TREATMENT OF ALZHEIMER'S DISEASE

Chairs: Bruno VELLAS (Toulouse, France), Ronald PETERSEN (Mayo, USA)

Monday 10.30 a.m. – 12.00 p.m. - Amphithéâtre Bleu

During this very important symposium on new, early-stage diagnostic methods and novel therapies, the speakers will provide an update on the **imaging of amyloid protein and the correlation between PIB** (Pittsburgh Compound B) images, **a new marker of amyloid deposits that can be used with positron emission tomography (PET) and biomarkers** (assay of the levels of amyloid protein and tau protein in the cerebrospinal fluid).

Nick FOX from London will compare **the usefulness of various early-stage diagnostic tools** (MRI, PET, amyloid markers, etc.) as part of therapeutic monitoring, and will try to **identify neuroradiological biomarkers that could enable assessments of disease progression during clinical trials using new compounds** that target amyloid protein or other lesions.

During the same symposium, Ronald Peterson, inventor of the MCI (Mild Cognitive Impairment) concept will raise the very important **issue of the populations to be targeted in clinical trials.**

Several other symposia will be dedicated to diagnostics: the ADNI symposium and symposium SB7 144 - FOR A NEW DIAGNOSTIC APPROACH OF ALZHEIMER'S DISEASE under the leadership of Professor Dubois from Paris, who will try to determine the best methods for early diagnosis.

New therapies

Different therapeutic approaches will be reviewed by Dale SHENCK from San Francisco during symposium SB 019 on the development of new therapies. The first researcher to perform immunotherapy trials in transgenic mice, Dale Schenck will emphasise the **importance of targeting not only amyloid protein but also other proteins:** tau protein, mitochondria and apolipoprotein E (APO E) as we know that one of its forms, APO E4, is a promoter of Alzheimer's disease.

Apathy, an extremely distressing symptom of the disease, will also be the topic of a session during symposium SC6 043-APATHY AND NEUROPSYCHIATRIC SYMPTOMS IN ALZHEIMER, chaired by Professor Philippe Robert from Nice. This session will be devoted to **defining, measuring and treating apathy.** One of the best treatments for this condition remains acetylcholinesterase inhibitors, while memantine relieves other types of behavioural disorders.

Cognitive stimulation

SC6 036 - COGNITIVE TRAINING IN LATER ADULTHOOD/ FINDINGS FROM FOUR INTERVENTION PROGRAMS

Chairs: Sherry Willis (Seattle, USA), Sylvie BELLEVILLE (Montreal, Canada)

Monday 14.00 p.m. – 15.30 p.m. Amphithéâtre Bleu

The usefulness of cognitive stimulation gave rise to many questions. A symposium will be devoted to this topic and involve Sherry Willis, who is leading the **most important study on cognitive stimulation, the ACTIVE study.** This study conducted in 2,800 healthy subjects has demonstrated that stimulation can improve cognitive functions and daily activities, and these effects are sustained for up to five years after training.

Other studies, carried out by the Max Planck Institute in Berlin, will also be presented. Research has focused on the working and episodic memories in subjects aged 20-30 years and 60-80 years. Not only did stimulation enable a more marked improvement in memory skills in young subjects than in elderly subjects, but it was also beneficial in elderly subjects. These results, measured using MRI, showed that the improvements perceived during neuropsychological tests were also accompanied by neuronal changes.

New approaches to prevention

Presentation of the European research consortium EADC (European Alzheimer's Disease Consortium)

SB8 175 - EUROPEAN ALZHEIMER DISEASE CONSORTIUM (EADC) INITIATIVE

Chair(s): Bengt Winblad (Stockholm, Sweden), Bruno VELLAS (Toulouse, France)

Wednesday: 10.30 a.m. – 12.00 p.m. - Amphithéâtre Bleu

Both therapeutic trials on investigational drugs and preventive studies require the structuring of research. Already ensured in the USA by the Alzheimer's Research Centers, this structuring has been implemented successfully in Europe with the EADC (European Alzheimer Disease Consortium). This network of excellence has enabled the conduct of a number of studies, such as the **ICTUS study** on the impact of cholinergic therapies on disease progression, or the **European multicentre study DECRYPTA**, the aim of which is to develop clinical diagnostic criteria for application at a pre-dementia stage.

SB7 099 - NEW APPROACHES IN AD PREVENTION

Chairs: Jacques TOUCHON (Montpellier, France), Serge GAUTHIER (Montreal, Canada)

Tuesday 10.30 a.m. – 12.00 p.m. - Amphithéâtre Bleu

Among the new preventive approaches reported, mention must be made of the **MAPT study (Multidomain Alzheimer Preventive Trial)**, a major, multicentre trial presented by Sophie Gillette from Toulouse University Hospital, that will be conducted in 1,200 frail elderly people aged 72 years or over in order to study the effects of a multiple approach to preserving cognitive functions: nutrition, physical exercise and cognitive and social activities. Enrolment is ongoing and the study is scheduled to last for three years.

Generally speaking, **the recommended preventive approaches involve cognitive stimulation, physical exercise and social integration**. Although highly promising, treatment approaches (the use of anti-inflammatory drugs, vitamin E and statins) have not so far proved their efficacy during controlled trials, but they remain very important from a theoretical point of view.

However, **the most promising approach is the management of cardiovascular risk factors:** particularly hypertension, but also atrial fibrillation, diabetes and hypercholesterolemia.

Two symposia will also be devoted to nutrition and brain ageing, one on antioxidant foods which has shown that consuming large quantities of fruits and vegetables, and more specifically polyphenol-rich foods (cranberries, strawberries, hazelnuts) would exert beneficial antioxidant and protective effects.

20 years of the PAQUID study

SB8 223 - **PAQUID: ALREADY TWENTY YEARS!** - Chairs: Pascale BARBERGER-GATEAU (Bordeaux, France), Jean-François DARTIGUES (Bordeaux, France)

Wednesday 17.30 p.m. -19.00 p.m. - Amphithéâtre Bleu.

The French epidemiological study PAQUID focused on functional and brain ageing, and was designed to estimate the prevalence and incidence of dementia, and particularly Alzheimer's disease, to identify risk factors for cognitive deterioration and to describe progression towards dependence. Initiated twenty years ago in 3,777 subjects aged 65 years or over in 75 towns in the Gironde and Dordogne regions, this study – initially conducted in subjects aged 65 years and then extended on the same cohort to 75 years – has yielded **important findings on the prevalence of Alzheimer's disease in France.**

The conclusions of follow-up have confirmed the initial figures: 850,000 people are probably affected in France by dementias of all types, 70% of them having Alzheimer's disease. Thus Alzheimer's disease and related disorders are responsible for 75% of dependence cases and 70% of care home placements.

This study has also demonstrated that the **first cognitive disorders** occur in those who will develop the disease **12 years before the onset of dementia**, and that a decline in visual and spatial memory and abstract thinking starts about 2 or 3 years previously. These conclusions confirm **the usefulness of neuropsychology as a very early diagnostic tool**, and provide very useful information regarding large-scale prevention. If a preventive therapy were available (e.g. a vaccine), the identification of early symptoms far upstream of disease onset could make it possible to target those in the general population with a very moderate impairment of certain cognitive skills, including verbal fluency, that do not have any effects on everyday life.

Finally, this study has also shown that the **determinants of dependence** (i.e. reduced mobility, limitations in instrumental activities and basic daily activities) are not only **age** but also the **onset of dementia**. It has also shown that **depression** is an additional factor for dependence.

National prevention plans

SD8 191- ALZHEIMER'S DISEASE AND RELATED DISORDERS: CROSS NATIONAL COMPARISON OF STRATEGIC ACTION PLANS

Chairs: Howard BERGMAN (Quebec Government Task Force on Alzheimer's disease and related disorders, McGill University and Jewish General Hospital, Montreal, Canada), Florence LUSTMAN (*Inspecteur général des finances*, commissioned by the French President to monitor the Alzheimer Plan in France)

Wednesday: 14:00 - 15:30 Amphithéâtre Bleu

This symposium will analyse and compare the strategic plans implemented in four different countries. Howard Bergman will present the Canadian plan, Joël Ménard from Université Paris Descartes will present the French plan, Henry Brodaty from the University of New South Wales (and one of the first to have suggested the implementation of an action plan in his country) will present the Australian plan, and S. Banerjee from King's College London will present the national plan implemented in the United Kingdom.