

ALZHEIMER'S

Alzheimer's disease is a neuro-degenerative illness that gradually but relentlessly destroys brain cells. It is the main cause of dementia among the elderly, affecting around 24 million people throughout the world.

It bears the name of Alois Alzheimer, the German neuropathologist who, in 1907, made the connection between dementia syndrome and its characteristic neuropathological lesions: senile plaques and degeneration of neurones, within which pathological filaments form.

Alzheimer's is a **chronic disease**. It is increasingly common among the public, **affecting the memory and mental faculties** in general. It is a disease that advances **progressively** and **irreversibly**, owing to **degeneration** of the brain tissue, eventually producing a state of dementia. In its most prevalent form, Alzheimer's generally appears **around the age of 60-70** and quite often remains undiagnosed. A more rare form of the disease, sometimes known as the early-onset family form, occurs before the age of 65 and, as its name suggests, has a pronounced inherited (genetic) component. With the aging of Western populations (Europe, USA), and in Japan, the disease will affect more and more people, and pose real problems over financial resources and labour supply in those countries.

Nearly 350,000 people benefit from care for the long-term complaint (ALD 25) of Alzheimer's-type illness and related diseases. Closely linked to the aging of the population and increased life expectancy, this affliction will continue its advance in coming years. The figures make Alzheimer's disease and related disorders a major public-health challenge. A start was made at taking better account of this with two action plans in 2001 and 2004. But the big challenge to be faced – with regard to medical research, dealing with the sick and support for families – demands resources that are equal to the scale of the challenge. Presented at the beginning of November 2007, the Alzheimer's plan for 2008-2012 mobilises public authorities and healthcare and social workers by proposing additional and innovative measures and resources.

The 2008-2012 Alzheimer's plan – Consult the Alzheimer's plan of 1 February 2008 (pdf format) at the government website – <http://www.premier-ministre.gouv.fr>

The commission charged with the task of drawing up the plan was chaired by Joël Ménard, a former healthcare manager. It includes ten members, selected for their knowledge of the disease. It is supported by the work of eight groups of experts. Each group has its own special topic. The main thrust of the 2008-2012 Alzheimer's plan is to focus on the ethical aspects of dealing with the disease, developing medical research, simplifying and improving the facilities available for the sick person and his/her family in every respect, improving care for cases of early-onset Alzheimer's (around 10,000 new cases every year aged below 60). The plan provides a budget of 1.6 billion euros over 5 years to improve the treatment of patients, also for research. The plan was presented by the Chairman as "a sustainable commitment by the State in a resolute battle against this disease".

Ten fundamental measures in the fight against Alzheimer's disease

Drawing on the work of the commission directed by Professor Joël Ménard, the plan aims to:

1. **improve diagnosis:** by elaborating and implementing arrangements to report and support; more consultations on activities that strongly involve the memory, etc.
2. **better care and support by opening a single service-point:** "Places for Autonomy and Integration of Alzheimer's patients", better co-ordination of help, increased home support.

3. **more and better help:** by developing and diversifying rest-and-respite facilities, putting in place a single phone number and website for information and local guidance.
4. **more rapid research:** by creating a scientific co-operation foundation to promote and co-ordinate scientific research.

21 September has been World Alzheimer's day since 1993.

In a decision of 27 July 2007, the Prime Minister decided to confer the "Grand National Cause" label on the campaign organised by the "Alzheimer's Association grand national cause" group of associations on the topic "Alzheimer's disease".

Alzheimer's – review

Worldwide, 26 million people suffer from Alzheimer's, and over 5 million in Europe. This figure could be multiplied fourfold by 2050. **Greater life expectancy means that in 2050 one person in every 85 will be struck down by Alzheimer's disease. Almost half of those sick people (43%) "will need extensive care and support "**, predicts Prof. Ron Brookmeyer of *Johns Hopkins University* in Baltimore, who has worked on this subject for some years.

The biggest increase in incidence will – unsurprisingly – affect the continent of Asia. According to Brookmeyer's estimates, 63 million cases will be registered in 2050. Against 12 million at the present time, i.e. a five-fold increase. **According to the Minister of Health, in France 800,000 people are affected by the illness and 165,000 new cases occur every year.** Figures that justified putting the Alzheimer's Plan in place. This is intended not only to step up efforts on **research, training and information.** It also needs to increase the number of memory consultations and places of accommodation.

(Source: *Johns Hopkins University* of Baltimore)

Patients' associations:

In France, the French Alzheimer's association – <http://www.francealzheimer.org/>

For Europe as a whole, the association is called Alzheimer Europe – www.alzheimer-europe.org – covering 31 associations in 27 countries.

In the USA: <http://alz.org>

Recent initiatives (June 2008):

The European Union is implementing a project aimed at developing diagnostic tools to enable early diagnosis of Alzheimer's disease.

There are several different types of dementia, but Alzheimer's disease is the most prevalent, representing 50% – 70% of all dementia cases. At the present time there is no treatment for, and no clear cause of, the illness.

PredictAD, a new EU-financed project, is under way; its task is to develop diagnostic aids, making it possible to predict Alzheimer's disease as early as possible.

Alzheimer's disease affects over 5 million people in Europe and over 24 million worldwide. According to estimates, that number is likely to double in the next 20 years. Alzheimer's generally affects people aged over 65 and is accompanied by a suite of most pernicious symptoms. To begin with, the loss of memory which, over months or years, produces crises of anger, hostility, volatility of mood, distancing by family and friends, and eventually a loss of bodily functions, followed by death.

At the present time there is no treatment to cure Alzheimer's. However, new medications go on the market all the time. Early diagnosis would make it possible to restore some hope to people suffering from the disease and to catch the disease in its early stages, before the symptoms become too severe, and hence irreversible.

This new research work relies on the development of tools to facilitate early diagnosis. At the present time, there is no test making it possible to predict whether a person is showing early symptoms of Alzheimer's disease, or is likely to develop the disease later in life. A full diagnosis can be carried out only in an autopsy.

PredictAD, a project funded with around 3 million euros and partners in six countries, will seek to perfect some indicators to allow Alzheimer's disease to be diagnosed following the study of imaging biomarkers (MRI, PET FDG and PET PIB), which measure electrical activity in the brain, also blood markers (proteomics and metabolomics), and to develop new ways of associating data from various biomarkers. The combination of these three new types of information will make it possible not only to perform early diagnosis of Alzheimer's disease, but will also help distinguish between the various types of dementia.

"According to latest estimates, the worldwide prevalence of Alzheimer's disease is expected to quadruple and reach 106 million people by 2050", reports Dr. Lennart Thurfjell, in charge of diagnostic software and medical diagnostics at GE Healthcare, one of the project's partners. "It's therefore essential to develop proper diagnostic tools in order to be able to carry out early diagnosis of this debilitating disease."

The project will run from June 2008 to May 2011. Later on, a specific biomarker will be used to perfect software that can be used by doctors to assess a predisposition to Alzheimer's disease and monitor its state of advance in patients, using data about them.

"PredictAD is aiming to develop an objective indicator facilitating diagnosis of Alzheimer's disease as early as possible", says Dr. Jyrki Lötjönen of VTT, scientific co-ordinator of PredictAD. "These diagnostics will become possible by virtue of the data from various data sources on the monitoring of patients, e.g. neuropsychological tests, medical imaging, measures of electrical activity in the brain and analysis of proteinic and metabolomic levels from blood samples. Early diagnosis will play a major role in effective treatment of Alzheimer's, especially in the future, once the new generation of treatments is available to patients."

"PredictAD chimes perfectly with the vision of 'Healthcare as early as possible' adopted by GE Healthcare, since the project will allow us to gain vital knowledge, not just about individual bio-markers, but also in relation to their combination with tools for early detection and to check the results of therapy. The fact of improving our understanding of the role that various bio-markers can play in the process of the disease, whether based upon imaging or not, is fundamental, while we are making very effort to perfect new diagnostic solutions for Alzheimer's disease," is how Dr. Thurfjell sums it up.

Public and private partners from eight research organisations, academics, industrialists and medics from four European countries, will form a research consortium. Members of the PredictAD consortium are the Centre of technological research of Finland (VTT), GE Healthcare (GB), Nextim Ltd. (Finland), University of Kuopio (Finland), Imperial College London (GB), University of Uppsala (Sweden), University of Milan (Italy) and Rigshospitalet (Denmark).

(Sources: www.vtt.fi; www.alzheimer-europe.org; www.gehealthcare.com)

Software for better diagnosis of Alzheimer's disease in the early stages

CNRS researchers at the Laboratory of cognitive neurosciences and cerebral imaging (CNRS / Pierre and Marie Curie University) have perfected image-processing software to facilitate automated measuring of the volume of the hippocampus, a brain structure that atrophies in the early stages of Alzheimer's disease. Thanks to a collaboration with Inserm researchers, the software has been used successfully to distinguish Alzheimer's patients from healthy individuals of the same age. In the future, this tool could effectively aid doctors in making an early diagnosis of the disease. This work is published in the July issue of the *Radiology* review.

Experts:

Prof. Joël Ménard, Professor of Public Health, specialist in cardiovascular disease, former director of health and chairman of the commission, which worked out the proposals that served as the basis the 2008-2012 Alzheimer's plan.

Professor Ronald Brookmeyer, Chair, Master of Public Health Program, *Johns Hopkins University* at Baltimore

André Syrota, General Director of Inserm

Prof. Jean-Claude Ameisen, Member of the National Consultative Committee of ethics, he chairs the Ethics Committee of INSERM.

Noël Renaudin, chairman of CEPS (Economic Committee of healthcare products)

Jean-Christophe Tellier, Chairman of Novartis France

Biotech firms and Alzheimer's:

118 laboratories, of which 80 biotech companies have targets not far from 150 molecules targeting MA. In France, 6 laboratories and 2 biotech companies have embarked on research programmes.

Some biotechnology companies working on approaches to Alzheimer's:

Addex Pharmaceuticals – www.addexpharma.com

Exonhit Therapeutics – www.exnhonit.com

Faust Pharmaceuticals – www.faustpharma.com

Helios Biosciences – www.heliosbiosciences.com

Innogenetics – www.innogenetics.com

Pharmaxon – www.pharmaxon.com

Pharnext – www.pharnext.com

Theraptosis – www.theraptosis.com

Trophos – www.trophos.com

2007 data (sources: LEEM):

- **Worldwide**
 - 118 laboratories, of which 80 Biotech companies are developing :
 - 148 molecules, of which
 - 57 are at pre-clinical phase
 - 42 are at phase I
 - 41 are at phase II

- **In France**

- 6 laboratories and 2 Biotech companies are developing :
- 29 molecules, of which
- 9 are at pre-clinical phase
- 5 are at phase I
- 6 are at phase II.

ALZHEIMER'S DISEASE

Alzheimer's disease is characterised by the presence of two types of cerebral lesion: amyloid plaques (an accumulation of peptide A β 42 in the inter-cellular spaces and neurofibrillar degeneration (i.e. accumulation of abnormally phosphorylated tau protein in the neurones). The two lesions can be associated: they are senile plaques, and characteristic of Alzheimer's disease.

While the number of products on the market is small, their therapeutic targets are many, and are the subject of a major research effort.

• Target no. 1: risk factors

In 10% of cases, Alzheimer's disease has a genetic explanation. In 1995, presenile genes 1 and 2 respectively were identified on chromosomes 14 and 1. These are responsible for increased production of peptide A β 42.

Secondly, form 4 of apolipoprotein E, which is involved in transporting cholesterol and the formation of amyloid plaques, is closely linked with the onset of Alzheimer's disease. Studies have shown that homozygotes for allele 4 are strongly (15 times more) predisposed to develop Alzheimer's disease.

Apart from this autosomal genetic form, Alzheimer's can be multi-factorial, and the risk factors form just as many targets on which a preventive strategy might act.

- Arterial hypertension.
- The metabolism: Acting on hypercholesterolaemia using statins; acting on diabetes and insulin resistance (linked to the level of β sanguin amyloid peptide) with Avandia. (**4 molecules under development**).

• Target no. 2: neuro-protection

These molecules form the interface between preventive therapy (as they delay the onset of neuronal lesions) and symptomatic therapy (as their aim is to slow down the advance of the illness).

We may classify these neuro-protectors by their mode of action:

- Strategies based on blocking the causal events of cytotoxicity, or those involved in neuronal death: acting on ROMs (Reactive Oxygen Metabolites) with destructive potential; acting on oxidising stress using IMAOs (**3 molecules under development**).
- Strategies based on stimulating potentially deficient endogenous protection processes using hormones, growth factors that mimic neurotrophic effects and which thereby stimulate neuronal survival (**14 molecules under development**).
- Repair strategies using cell and gene therapies (**3 molecules under development**).

• Target no. 3: the pathological process itself

This entails getting at the process of Alzheimer's itself, and on its causes, for a curative therapy.

Some molecules have an upstream action on the production of peptide Abeta 42: by inhibiting secretins β and gamma, which are responsible for the production of this peptide (**8 molecules under development**).

Others act directly on the peptide: these involve vaccines (**3 molecules under development**), monoclonal antibodies (**10 molecules under development**) or a neutraliser agent (SALA: Selective Amyloid Lowering Agent) (**1 molecule under development**).

Some molecules will prevent the formation of amyloid plaque: by fixing the glycosaminoglycans required for formation of the plaque, by chelating the ions involved in formation of the plaque; or by destroying it.

In the case of the degenerative process that involves the tau protein, research is in progress, the targets studied being the enzymes responsible for the hyperphosphorylation of tau proteins.

- **Target no. 4: the symptom cluster**

At the more advanced stages of the illness, this involves applying methods capable of alleviating the deficits caused by the disease.

- **Acetylcholine deficit:**

Alongside molecules already on the market, namely 3 acetylcholine esterase inhibitors (ARICEPT®, EXELON®, REMINYL®) and an NMDA antagonist (EBIXA®), other acetylcholine esterase inhibitors, capable of offsetting this deficit, are under development (**6 molecules under development**). Muscarine and nicotine receptor agonists, which stimulate acetylcholine production, are also under development.

- **Cognitive deficits:**

Using NMDA (N methyl Daspartate) receptor antagonists, which combat an accumulation of glutamate. Action on the memory with calcium pathway antagonists and AMPA receptor agonists (alpha amino 3 hydroxy 5 methylisozazol4propionate; action on GABA receptor (gamma-aminobutyric acid) (**18 molecules under development**).

- **Local inflammation:**

This entails tackling local inflammation in order to reduce neuronal destruction using AINS (**4 molecules under development**).

(Sources: LEEM)