Alzheimer's Disease

Scientific, medical and societal implications

Synthesis and recommendations

Collective expert report
Inserm (French National Institute for health and medical research)

This document presents the synthesis and recommendations of the group of experts assembled by Inserm (French National Institute for health and medical research) as part of the collective expert report procedure (Appendix 1) set up in response to the request made by the French Authority General of Health – *Direction générale de la santé* (DGS)[a] concerning Alzheimer's disease and its scientific, medical and societal implications. This work is based on the scientific data available in the first half of 2007. The documentary base of this expert report is made up of some 2,000 articles.

This collective expert report was coordinated by the Inserm Collective Expert Report Centre.

[a] In relation with the Strategic Analysis Centre – Centre d'analyse stratégique (ex-Commissariat général du Plan)

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Preface

Confronted with the human and medical challenges thrown up by Alzheimer's disease, Inserm *(Institut National de la santé et de la recherche médicale)* is strengthening its commitment in all areas of research devoted to this condition. Numerous Inserm teams and laboratories, heavily committed to both fundamental and clinical research, have been instrumental in pushing forward the boundaries of knowledge in recent years. But if further progress is to be made, the scientific community will need to adopt a multidisciplinary approach incorporating all the neurosciences, the humanities and social sciences, epidemiology and health economics. Teams already active in these fields must strive even harder to organize themselves into networks, in particular regional centres of excellence combining complementary skills. Experiments involving major multidisciplinary research programs on a European and international scale will help to forge ties of partnerships between research institutions, and between the academic and private sectors. The challenge ahead is enormous!

Inserm has responded positively to the French Health Department's request for a collective expert report on the scientific, medical and societal implications of Alzheimer's disease. The findings and recommendations, based on the analysis of the international data available at the present time and set out at the end of this research work, will provide the main avenues of research for a better understanding, treatment and prevention of this disease.

This expert report could hardly come at a more opportune time since the Government has launched a commission chaired by Joël Ménard, former Director General of Health, charged with drawing up an action plan against Alzheimer's disease. The commission's preliminary guidelines were published on 21 September 2007.

The growing frequency of the disease is a cause for concern for both policy-makers and society as a whole. Epidemiological studies should give an estimation of the true prevalence of Alzheimer's disease in France so that the necessary steps can be taken to provide for its treatment. The cohort studies currently underway hold out great promise for determining the risk factors, targets for future preventive initiatives.

At the same time, and despite the fact that the disease represents an economic challenge of the first magnitude, there is still a shortage of health economics research teams focusing on this question. And yet they have a key role to play in advising the public authorities on the introduction of new forms of treatment or health care policies.

The experts convened by Inserm point to the need to improve early diagnosis. The development of new tools in the field of neuropsychology, capable of exploring the cognitive functions affected by Alzheimer's disease, advances in neuroimaging (functional magnetic resonance imaging or molecular imaging) enabling us to quantify the extent of injuries, and the search for biomarkers of the condition – these are all lines of research for the improvement of early diagnosis. But progress in this field must be envisaged alongside the development of more efficient and effective treatments.

This is quite clearly a point of crucial importance. Fundamental research (genomics, transcriptomics, proteomics, structural biochemistry, cellular biology, etc.) must provide a better understanding of the pathophysiology of this disease and point the way towards new potential treatments. As for the etiology of Alzheimer's disease, our knowledge of the risk factors, albeit partial, has moved forward and opened up prospects for prevention.

New research in the social sciences and the humanities should help to give decision-makers, health care professionals and the population as a whole a different image of the disease. Progress in all the approaches listed above must serve the purpose of providing the best possible treatment consistent with the respect and dignity of those suffering from Alzheimer's disease.

Christian Bréchot
Director General of Inserm

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Foreword

In France, as almost everywhere else in the world, Alzheimer's disease affects a large proportion of the population, i.e. about 6% of people over the age of 65. It is estimated that more than 850,000 people are currently suffering from the disease, a majority of them women, and each year some 225,000 new cases appear.

Wrongly considered to be a result of the ageing process, Alzheimer's disease was, for a long time, overlooked by policy makers. Although the situation in this respect has improved considerably in recent times, the general population still tends to take a very fatalistic view of the disease. With regard to health care and research, Alzheimer's disease does not benefit from the same level of priority as diseases affecting younger adults. And yet this condition, particularly in its advanced stages, confronts our society with a major ethical challenge inasmuch as it requires us to maintain ties of solidarity with the afflicted.

The public authorities have introduced successive governmental plans (2001-2004 and then 2004-2007) chiefly aiming to improve the quality of life for patients and their family circle. A recent report by the Parliamentary Office for the Evaluation of Health Policies - *Office parlementaire d'évaluation des politiques de santé* (Opeps, 2005) analyzed the regulatory legislative system (health, social and community health component) and government action (specific plans, etc.), together with the various decrees and *circulaires d'application* implementing these plans.

Recognizing Alzheimer's disease as a national cause on the same footing as cancer should lead to a greater willingness on the part of the public at large to take responsibility for its treatment. In spite of a greater knowledge of the pathophysiology, the risk factors involved and the development of the disease, medical practitioners remain poorly informed as to the specific features of Alzheimer's disease and the health care to be prescribed to patients. There is still much hesitation surrounding the use of treatments whose effectiveness is difficult to assess in the context of an evolving disease. The gradual deterioration of mental faculties and physical capabilities associated with the disease calls for a long-term multimodal approach. The persons close to the patient and all those involved in providing assistance on a daily and informal basis often feel that they receive little support. Much remains to be done in building up a uniform network in terms of information, diagnosis, means and the coordination of health care and community health management.

Support for institutional research is still limited despite the fact that the advances made could have major repercussions for an improved understanding, treatment and prevention of the disease. It is important, too, not to overlook research in the humanities and social sciences as these can help to meet people's short-term needs.

The French Authority General of Health[b] wishes to be able to call upon, via the Inserm collective expert report procedure, a review of the advances made in fundamental and clinical research, as well as in the humanities and the social sciences, on the subject of Alzheimer's disease, as a prelude to launching a prospective reflection on the essential changes to be made in the short, medium and long-term management of the disease.

Inserm has assembled a multidisciplinary group of 15 experts focusing on the following issues:

[b] In relation with the Strategic Analysis Centre – Centre d'analyse stratégique (ex-Commissariat général du Plan)

- What are the advances in research facilitating the definition and study of Alzheimer's disease? What is the state of knowledge in neuropathology, cellular and molecular biology, genetics and neuropsychology? What are the contributions made by brain imaging? What are the prospects for innovation in pharmacology and immunotherapy?
- What progress has been made in the sphere of diagnosis? What advantages are procured by early screening? Which tools have been validated?
- What is the significance of the symptoms associated with cognitive deficits?
- What are the evaluation methods and the effectiveness of the pharmacological treatments?
- What are the evaluation methods of the effectiveness of the non-pharmacological treatments?
- What is the place of informal aid and how is the role played by helpers evaluated in the care of patients?
- What is the extent of Alzheimer's disease in France? What are the data with regard to prevalence and incidence? What are the trends?
- What are the risk and protective factors liable to come into play in the onset and evolution of the disease? Can preventive actions be envisaged?
- What are the data concerning access to diagnosis and care in the population? How can the health care procedure be improved?
- What are the sociological data which could shed light on public health initiatives?
- What approaches enable us to appraise the economic problem posed by the disease? (care, health care systems)?
- What are the public health policies with regard to this condition? What direction should the governmental programs take in the light of the new data in the fields of science, medicine, the humanities and the social sciences?

In the course of twelve working sessions, the group of experts carried out a critical analysis of the current data on the basis of some 2,000 scientific publications and various national and international reports. The group concentrated its effort on Alzheimer's disease and not on dementia as a whole. The term dementia, when applied to Alzheimer's disease, is harmful to its image and its specificity, and it should be possible to avoid its use in the future.

The group of experts auditioned several persons addressing difficult questions concerning the evaluation of symptomatic medicinal treatments and their efficacy, as well as the ethical and legal aspects related to the disease. It also became acquainted with the missions of the National Solidarity Fund for Autonomy -*Caisse nationale de solidarité pour l'autonomie* (CNSA), a new administrative public body designed in particular to finance assistance for old and disabled persons. Lastly, it set great store by its discussions with the France Alzheimer Association concerning the importance of being mindful to the needs of patients and their families.

Following on from the expert report, the group of experts issued certain proposals for improving the dissemination of knowledge, the early diagnosis of the disease, the treatment of patients and support for helpers, within the context of an improved global heath care strategy. The group pinpointed certain areas of research for gaining more extensive knowledge of the etiology and the underlying mechanisms of the disease, with a view to discovering new and potentially more effective therapeutic approaches. Finally, it

emphasized the need to develop research in the economic and social sciences for this disease with its many societal repercussions.

Synthesis

Alzheimer's disease was first described one hundred years ago. With the increase in life expectancy, especially in developed countries, its incidence has increased dramatically and current forecasts speak in terms of a doubling of the number of persons affected every 20 years.

Alzheimer's disease is the most frequently encountered form of dementia (about 70% of cases of dementia). The earliest and most frequent manifestations are benign memory disorders relating to recent facts and, in most cases, concerning details of everyday life. There is then a slow evolution of the symptoms which will gradually spread to organizational and programming disorders (executive functions), language difficulties (aphasia), clumsy gestures (apraxia) and defective recognition of objects, places and persons (agnosia). The disease is also accompanied by various disorders that exacerbate the cognitive disorders and may serve to put the tolerance of the patient's family circle under severe strain: withdrawal, apathy, depressive symptoms, sleep and appetite disorders, agitation, hallucinations, etc. Finally, somatic neurological signs usually occur, leading to balance and walking disorders, and an increased risk of falls. Alzheimer's disease, perceived as a slow and inexorable intellectual and physical deterioration, sends a very negative image to society.

One of the aims pursued by clinicians is to identify patients suffering from cognitive disorders not yet having an impact on daily activities or autonomy. These disorders may be considered as a first symptomatic phase of Alzheimer's disease. The most commonly used term to define the condition of these patients is Mild Cognitive Impairment (MCI). These patients present a higher risk of developing a demential syndrome after one or more years of follow-up.

There is a minority of cases of monogenic family transmission (about 1% of patients) occurring at a much earlier stage, sometimes even before the age of 40. In most cases, Alzheimer's disease appears as a multifactorial disease resulting from the interaction of various environmental, epigenetic and genetic factors that might facilitate its onset. Various studies have identified "risk factors" and "protective factors". Cardiovascular factors like high blood pressure would be examples of the former, while a healthy lifestyle (physical and intellectual activities, fish consumption, etc.) would seem to have protective effects.

Today, in France, the diagnosis of Alzheimer's disease is made at a late stage and treatment of patients varies considerably. The symptomatic drugs currently available have only a modest (and sometimes disputed) effect on the evolution of the disease. Other resources exist, seeking to stimulate and consolidate the patient's functions, to improve his well-being and ability to fend for himself, and to provide support for his family.

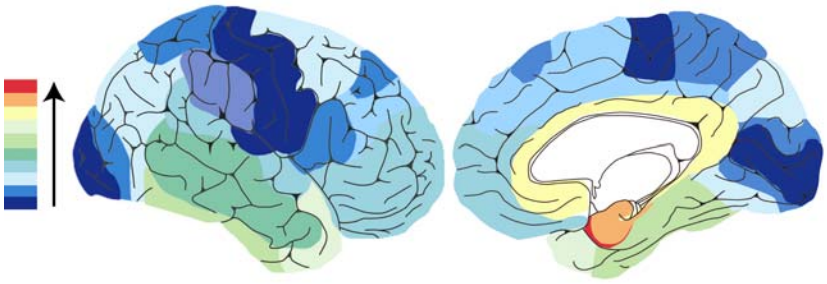
Lastly, in addition to the heavy burden of the disease itself, the financial cost – for families and for society – is by no means negligible, and it is essential to make economic projections on the basis of the different scenarios that seem likely today.

Alzheimer's disease is characterized by brain lesions

The definitive diagnosis of Alzheimer's disease is based on the observation of characteristic brain lesions (usually found during a post-mortem examination): senile plaques and neurofibrillary tangles. These microscopic alterations are associated with macroscopic modifications. The weight and volume of the brain are reduced on average. Cortical areas playing a role in the memory functions and located on the internal face of the hemispheres – the entorhinal cortex and the hippocampus – are the first to lose volume, followed by the regions of the cortex implicated in such functions as language, the complex analysis of visual or auditory impulses or the programming of voluntary movements.

Microscopic examination reveals two lesion types – neurofibrillary and amyloid. Each of these lesions is located in specific areas of the brain.

The neurofibrillary pathology is due to the pathological accumulation in the neuron of a naturally present protein, the tau protein. This protein plays a role in the polymerization of the microtubules, while the amyloid pathology is characterized by the extracellular accumulation of a peptide which is normally present in low concentrations: amyloid-beta peptide (Aβ). The normal function of this peptide, and of its precursor, remains unknown.



Density map of the neurofibrillary lesions of Alzheimer's disease according to topography (from Duyckaerts and Dickson, 2003)

The color scale runs from the least to the most severely affected. Note the very severe (red) condition of the transentorhinal cortex, the marked condition (fawn) of the entorhinal cortex and the respect of the primary sensory areas (dark blue).

The accumulations of Aβ peptide and tau protein assume different morphological aspects. The extracellular Aβ peptide may form voluminous, weakly concentrated deposits in a "geography map": diffuse deposits.

The focal deposits of Aβ peptide are, by contrast, dense and spherical in form.

Their physico-chemical characteristics are peculiar to amyloid substances: insolubility in the usual solvents, fibrillary structure in electronic microscopy and affinity for certain stains such as Congo red or thioflavin. The Aβ peptide is also deposited in the vessel walls (amyloid angiopathy). Neurofibrillary tangles correspond to the aggregation of tau protein in the cellular body of the neuron. Neuropil threads are nerve extensions, for the most part dendritic, loaded with tau protein. This protein also accumulates in the axons surrounding the focal deposits of Aβ peptide, forming the crown of the senile plaque. The senile plaque is thus made up of a focal deposit of Aβ peptide surrounded by a crown of axons enriched in tau protein.

With regard to the topography of the lesions, the neurofibrillary pathology preferentially affects the entorhinal cortex, the hippocampus and associative areas. It also affects subcortical structures: the limbic nuclei of the thalamus, the basal nucleus of Meynert ensuring the cholinergic innervation of the cortex, the locus ceruleus (noradrenergic innervation) or the raphe nuclei (serotoninergic innervation). Diffuse and focal deposits of

Aβ peptide are observed in the cerebral cortex. Deposits of diffuse type only are observed in the central grey nuclei and the cerebellum.

Thanks to the analysis of a large number of cases, of varying age and severity, it has been possible to trace the spatial and temporal evolution of the lesions, and to describe the different stages. The neurofibrillary lesions concern successively the entorhinal (Braak stages I and II), hippocampal (stages III and IV) and neocortical (stages V and VI) regions. Each stage adds a new affected structure to those affected at the previous stage. The same applies to Thal's 5 "phases" describing the evolution of the Aβ peptide deposit which occurs successively and additively in the neocortex, in the entorhinal area and the hippocampus, in the subcortical nuclei, in the brain stem and finally in the cerebellum.

The progression of the neurofibrillary lesions in the cortex (entorhinal cortex, then hippocampus and lastly neocortex), corresponds to the progression of the symptoms. On the other hand, the deposits of peptide Aβ are less well correlated with the symptoms. It is quite common to find, in elderly subjects considered to be intellectually normal, diffuse deposits of Aβ peptide in the cerebral cortex associated with neurofibrillary degeneration in the hippocampus and the entorhinal cortex. These lesions appear constant in the brain of centenarians on whom a post mortem examination has been performed. They can be found in young subjects considered to be asymptomatic. Their significance is a matter of debate. Their frequency is seen by some people as the indication that they could remain stable and that they testify solely to physiological cerebral ageing, a somewhat imprecise concept. According to another hypothesis, these lesions, even if they are without clinical consequence, could signal the presence of an as yet asymptomatic Alzheimer's disease.

There are still many unknown factors in the neuropathology of Alzheimer's disease and its clinical correlations, in particular because of the paucity of systematic post-mortem studies of patients suffering from Alzheimer's disease and of normal old persons (especially in France). The most commonly accepted hypothesis today of the amyloid cascade suggests that deposits of Aβ peptide lie at the root of the neurofibrillary pathology. Why then, in this hypothesis, do we observe, in the early stages, neurofibrillary lesions without amyloid deposits? Can the Aβ peptide accumulate in the parenchyma before the senile plaques are formed? What is the relationship between the pathology linked to the Aβ peptide and that associated with the tau protein?

Using transgenic mice expressing one or different genes covering one or more mutations responsible for "family" (i.e. non-sporadic) Alzheimer's disease, it is possible to understand, under experimental conditions, certain stages of the pathology: amyloid deposits have never been at the origin of an intracellular accumulation of tau protein in the mouse, and vice versa. It is therefore essential to confront the complexity of human neuropathology with its animal models.

Moreover, very few studies involving large cohorts of patients on whom autopsies have been performed have been devoted to the pathological correlates of MCI and symptoms such as behavioral disorders, extrapyramidal syndrome, sleep disorders and weight loss. The epidemiology of the lesions of Alzheimer's disease is still little known, most studies involving hospital patients. What is the situation with regard to the general population? What is the frequency, probably underestimated, of the lesions themselves and the associated vascular or neurodegenerative pathologies (in particular Lewy bodies found in Parkinson's disease and dementia with Lewy bodies)? Thus many questions, involving the systematic collection of data obtained by post-mortem examination of brains, have yet to be explored.

The cerebral lesions are accompanied by an accumulation of amyloid-β peptide

As described previously thanks to post-mortem examinations, Alzheimer's disease is characterized by deposits of various morphologies, of specific topology and apparition kinetics, referred to as diffuse deposits, focal deposits and vascular deposits. All these cerebral lesions are made up of hydrophobic peptides of various kinds, grouped together under the generic term of amyloid peptides (Aβ) and all derived from a precursor called βAPP (β-Amyloid Precursor Protein) or APP. The purification of the Aβ peptide in 1984 and the cloning of its precursor in 1987 resulted in a major leap forward in the understanding of the genesis of this peptide. In particular, it showed that Aβ peptide is a "normal" catabolite of the physiological maturation of βAPP. Post-translational alterations affect the levels of Aβ peptide in the cell. When the amount of Aβ peptide increases, the hydrophobic peptide is aggregated and the process of peptidic deposits is probably initiated. Certain mutations, responsible for genetic, aggressive and early forms of Alzheimer's disease, have been identified on βAPP itself. Interestingly, these mutations always trigger an alteration of the levels or the very nature of the Aβ peptides. This goes to show the importance of the Aβ peptide in the etiology of Alzheimer's disease and underlines the interest of studying the enzymes responsible for the formation of the amyloid peptide. The Aβ peptide is the result of the combined action of two distinct proteolytic enzymes, β-secretase and γ-secretase, respectively releasing the N- and C-terminal extremities of the peptide. This constitutes the amyloidogenic route.

The activity of β-secretase is now well characterized. It is an acidic protease, simultaneously purified and characterized by several research teams, and called BACE1 (β-site-APP Cleaving Enzyme 1) or memapsin 2. The BACE1 protease possesses a homolog named BACE2 which does not seem to be very present at cerebral level and which makes little or no contribution to the production of Aβ peptide. The invalidation of the gene coding for BACE1 is on its own enough to block virtually the entire production of Aβ peptide. The mice invalidated for BACE1 are viable and fertile.

γ-secretase is the enzyme which releases the C-terminal extremity of the amyloid peptides, generating the couples Aβ40/AICDC59 (Amyloid IntraCellular Domain) and Aβ42/AICDC57. Another cleaving (cut ε) takes place upstream of the γ-secretase, close to the internal layer of the membrane, which releases the AICDC50. Numerous studies suggest that presenilins 1 and 2 (PS1 and PS2), the proteins responsible for most of the familial forms of Alzheimer's disease, are themselves carriers of the γ-secretase activity. The first elements pointing in this direction concern the empirical observation that the mutations brought about by the presenilins always modulate the levels and nature of the Aβ peptide formed, with a particular incidence on the exacerbated production of pathogenic Aβ x-42. Furthermore, the invalidation of the gene coding for PS1 drastically reduces the production of Aβ peptides, and this production is virtually eradicated when both PS1 and PS2 are reduced. The γ-secretase activity depending on the presenilins appears to be carried by a multiproteic complex of high molecular weight implicating at least three other proteins: nicastrin (NCT), Aph-1 (Anterior pharynx defective 1 homolog) and Pen-2 (Presenilin enhancer 2 homolog). There are two presenilins, three homologs of Aph-1 (Aph-la, Aph-lb and Aph-lc) and two isoforms of Aph-la (Aph-laL and Aph-laS). The existence of distinct γ-secretase complexes no doubt reflects the fact that each of them could have a different function linked to the capacity to hydrolyse specific substrates.

The endogenous levels of Aβ peptides are governed by the balance between the peptide-forming and the peptide-degrading processes. There are no studies showing that the

amyloid peptide formation processes are altered in the sporadic forms of Alzheimer's disease; in particular, no study has established that the activities of β- and γ-secretases were increased. It is accepted that the modifications leading to the increase of Aβ peptide levels are generally post-translational. The peptide-degrading processes are thus of particular importance. Studies concerning the Aβ peptide-degrading enzymes have identified neprilysin (NEP), the endothelin conversion enzyme (ECE) and the insulin-degrading enzyme (IDE), both of which could constitute therapeutic targets.

Neurofibrillary tangles result from the aggregation of the tau protein

In Alzheimer's disease, neurofibrillary degeneration results from the intraneuronal aggregation of tau proteins in the form of pairs of helix filaments. The presence of these neuropathological lesions is very well correlated with cognitive deficits.

Tau proteins are proteins associated with microtubules. They are mostly expressed in neurons. There are six isoforms of tau protein in the adult human brain generated by alternative splicing from a single gene located on chromosome 17. These proteins play a role in the polymerization and stability of the microtubules. This function is regulated by the state of phosphorylation of the tau proteins.

In many neurodegenerative diseases (grouped together under the term "tauopathies"), abnormally phosphorylated tau protein isoforms are aggregated in filaments. In Alzheimer's disease, neurofibrillary degeneration is initially found in the entorhinal cortex and the hippocampal formation, sequentially affecting neuronal sub-populations of the isocortex. It then appears in the associative polymodal regions, followed by the associative unimodal regions and finally by the primary and secondary sensory-motor regions. In the other neurodegenerative diseases, there is an aggregation of the tau proteins not only in neurons but also in glia cells.

Hyperphosphorylation and the change in the ratio between the different tau protein isoforms are of crucial importance in the formation of neurofibrillary tangles. From an etiological point of view, tau splicing may be modulated directly (mutations on the tau gene in some familial forms of frontotemporal dementia associated with a Parkinsonian Syndrome) or indirectly (repetitions of CUG triplets in Steinert's myotonic dystrophy). As for the abnormal phosphorylation of tau, this may result from the increased activity of certain kinases (kinases depending on reduced phosphatase activity) and from the modulation of regulators (peptidyl-prolyl cis-trans isomerase activity, proteins 14.3.3, etc.). The modifications leading to the aggregation of the tau proteins are therefore phosphorylation and variations in splicing. These modifications would appear to be the cause of a change in protein conformation.

There are also tau protein aggregation co-factors such as glycosaminoglycans and fatty acids which could facilitate the formation of fibrils. Other avenues are also being explored in an effort to understand the conditions leading to neurofibrillary degeneration. Mention may be made here of oxidative stress, the reactivation of the cell cycle and the vulnerability of specific neuronal sub-populations. The potential therapeutic strategies are based on these etiological hypotheses.

The aggregation of the tau proteins upsets neuronal functioning. While the alteration of axonal transport constitutes the principal disturbance, there are other, as yet poorly understood consequences, such as the deficit in neurotrophic and neurotransmitter agents.

Identification of the various genetic factors can provide a better understanding of the causes of the disease

Although we are now beginning to have a better knowledge of the mechanisms liable to lead to the lesions characteristic of Alzheimer's disease, we are still far from understanding them completely. It is in fact a major challenge to characterize the factors capable of facilitating the development of a complex pathology like Alzheimer's disease. Several kinds of factors may be involved – genetic, epigenetic and environmental – and a person's predisposition to develop the disease will depend on the interaction of these factors. However, since Alzheimer's disease appears to be a disease with a by no means negligible genetic predisposition, considerable efforts to characterize its genetic determinants have been made over the last twenty years.

It is estimated that less than 1% of cases present an autosomal dominant mode of transmission, such forms being early (<60 years) or very early (<40 years). Over and above these familial monogenic forms, a clear familial aggregation may exist in about 5 to 8% of cases. The existence of a family history for these forms is associated with an increase of 2 to 5 times in the risk of developing Alzheimer's disease. On the other hand, no familial aggregation is known in over 90% of the cases of Alzheimer's disease, essentially when the disease develops at a later stage (65 years +). These latter forms are defined as "sporadic" and could be taken to imply the absence of genetic determinism. However, it has now been clearly established that genetic factors may in fact be implicated in these sporadic forms. Thus, whether in the forms presenting a familial aggregation or in the sporadic forms, Alzheimer's disease appears as a multifactorial pathology resulting from the interaction of genetic and environmental factors. In conclusion, all of the non-monogenic forms of Alzheimer's disease are defined as not presenting a classic Mendelian transmission.

The discovery of mutations responsible for the autosomal dominant, and therefore monogenic, forms of Alzheimer's disease has had a profound impact on our understanding of the pathogenic process of the disease. In 1991, the first mutation on the gene of the amyloid precursor protein (APP) was identified. This is the protein whose metabolism produces the amyloid peptides which are the principal components of the amyloid deposits. Then, in 1995, mutations on the genes of presenilins 1 and 2 (respectively PS1 and PS2) were brought to light. These mutations, in particular those of PS1, were very soon associated with an increase in the production of amyloid peptides, more specifically by facilitating the Aβ x-42 forms. The characterization of these mutated forms helped considerably in placing the metabolism of the APP at the centre of the pathological process of Alzheimer's disease and in advancing the hypothesis of the amyloid cascade.

However, although there can be no denying the importance of the mutations of APP, PS1 and PS2 genes, these mutations do not explain all the existing monogenic forms of Alzheimer's disease and, most of all, they are only responsible for very rare forms of the pathology.

As far as the forms without classic Mendelian transmission are concerned, the major impact of ε4 allele of the gene of apolipoprotein E (APOE4) on the risk of developing Alzheimer's disease was revealed in 1993. Individuals with at least one copy of this allele have a risk that is 3 to 4 times greater of developing the disease, with an earlier onset. The APOE4 gene would appear to be associated with about 20% of cases of Alzheimer's disease. Nevertheless, the implication of the APOE protein in the physiopathological process has yet to be elucidated.

This first and essential discovery gave rise to hope that the study of the genetics of the forms of Alzheimer's disease without classic Mendelian transmission would not take very long to

complete. However, since this discovery, and despite the proliferation of analyses (nearly 200 candidate genes studied, and more than 800 publications devoted to them), no consensus has been reached as to the characterization of new genetic determinants of the disease. It has nevertheless been estimated that there are at least 4 major genes with a similar effect to that of the APOE. Moreover, thanks to an analysis of the genetic liaisons on the forms with a family aggregation, more than 20 loci have been characterized, which may contain a genetic determinant of Alzheimer's disease. A consensus has been established for 4 chromosomal regions in 9p21, 9q22, 10q21-25 and 12pll-12. It is therefore likely that several dozen genes, presenting a more modest effect, are also involved.

In other words, a large majority of the genetic component of Alzheimer's disease has yet to be characterized. But new horizons are opening up thanks to the emergence of new high-speed approaches making it possible to analyze thousands of polymorphisms in a short lapse of time, and at a low cost per genotyping. Moreover, major new advances should result from the establishment of biological convergences for selecting the most relevant candidate genes.

The characterization of these genes should foster understanding of the pathophysiological process(es) involved in the development of Alzheimer's disease. And this understanding will in turn contribute to the development of new therapies by targeting key proteins of the pathophysiological process. Individual genetic profiles could potentially be established in order to define the most effective therapeutic care. In this connection, it has been reported that the effectiveness of the acetylcholinesterase inhibitors would depend on the APOE genotype, the individual carriers of the ε4 allele responding less well to the treatment. Finally, it has to be said that a genetic tool for diagnosis will only prove possible once we have an exhaustive knowledge of the actors involved in Alzheimer's disease.

Research advances pave the way to new therapeutic approaches and new biomarkers

The treatments in use today are based on previous observations: Alzheimer's disease is accompanied by a fall in the level of acetylcholine in the brain; hence the idea of acting on the enzyme responsible for the degradation of this neurotransmitter (anti-acetylcholinesterasic strategy) or, more recently, with another medicine acting on glutamate, a neurotransmitter having a neurotoxic effect at high concentrations (anti-glutamatergic strategy).

Thanks to the progress made in our understanding of Alzheimer's disease, it is now possible to consider new therapeutic approaches. Most of these strategies amount to trying to prevent the accumulation of amyloid β-peptide (Aβ) or its fragments.

Immunotherapies have been carried out on transgenic mice (which mimick the consequences of the human pathology). Two types, active and passive, have been tested in the animal. In the case of active immunotherapy, the injection of aggregated Aβ 1-42 peptide, or of fragments, induces an immune response which prevents the apparition, or reduces the quantity, of amyloid deposits. The effectiveness of this treatment varies according to the type of peptide used, the administration route, the amyloid pathology and the model used. Similar results are obtained with passive immunotherapy, which consists in administering monoclonal antibodies directed against the Aβ peptide.

The mechanisms underlying the clearance of the amyloid deposits in the brain of transgenic animals, following immunotherapy, are as yet poorly understood. After active immunization, the disappearance of the amyloid deposits in mice was associated with an improvement of their performance in spatial memory tasks. Similarly, passive immunotherapy in old transgenic animals, although having a weak effect in reducing the

amyloid charge, nevertheless led to a significant improvement of the cognitive functions. Other biological parameters linked to cognition, such as synaptic integrity, are also improved by immunotherapy.

These approaches have opened up the prospect of therapeutic strategies in the human. The first attempts in this direction were carried out in 2001, but had to be abandoned when 6% of the patients contracted meningoencephalitis.

Meanwhile, pre-clinical trials have resumed in the animal, seeking an immunotherapy presenting fewer side effects and an approach more targeted towards pathological forms of the amyloid peptide. Most of these approaches are still in pre-clinical trials but some of them are in phase I or II, and one is already in phase III. Immunotherapy is unquestionably the therapeutic innovation which holds out most hope for the treatment of Alzheimer's disease.

Parallel to this, genic invalidation studies of β-secretase (BACE1), which releases the N-terminal extremity of the Aβ peptide, have shown that animals deprived of BACE1 are viable and fertile, and do not present any major phenotypic alterations. However, the crystallization of BACE1, associated with its substrate, has shown that the site where the substrate is linked to the enzyme is very extensive, making it difficult to sustain the conception of non-peptidic, bioavailable and metabolically stable inhibitors. Thus, no β-secretase inhibitors have currently reached the clinical trial stage. There are two other approaches, consisting either in reducing the BACE1 levels by an antisense RNA approach or in blocking the accessibility of the enzyme of the amyloid β precursor protein (βAPP) with the help of specific antibodies. This latter approach, still in the experimental stage, makes it possible to ignore the fact that BACE1 can split other substrates apart from βAPP and allows the enzyme to remain operational for its other functions.

γ-secretase, which releases the C-terminal extremity of the Aβ peptide, is a key theoretical target if the excess production of this peptide is to be blocked. The γ-secretase activity encompasses two types of enzyme complexes, dependent or independent of the presenilins (PS). Problems rapidly arose with the strategy seeking to block the PS-dependent complex, since the genic inactivation of the PS was lethal *in utero*. However, an inhibitor (LY450139) has recently been described for which the authors do not report any pronounced toxicity in a clinical trial of short duration. But no significant fall in the level of Aβ peptide levels has been measured in the cerebrospinal fluid.

α-secretase splits the βAPP in the middle of the Aβ sequence, and in theory reduces the production of the Aβ peptide. It has been established that activators of protein kinase C increased the α-secretase split, resulting in a reduction of Aβ peptide *in vivo*. The challenge is thus to develop agents which stimulate α-secretase. Some promising results have been obtained: bryostatin reduces the accumulation of Aβ peptide in the brain of transgenic mice without immediate side effects.

The degradation of Aβ peptide is also a target worth pursuing. The major enzymes participating in the catabolism of the peptide are neprilysin (NEP), the endothelin converting enzyme (ECE) and the insulin-degrading enzyme (IDE). Various options may be considered for their pharmacological activation.

There are several strategies seeking to block the polymerization of the Aβ peptide and thus its aggregation. Two candidate molecules, Alzhemed™ (or tramiprosate) and Clioquinol, are now undergoing clinical trial. The aggregation processes are amplified by the heavy metallic ions, and the chelators of these ions may therefore delay polymerization.

It has been shown that glycosaminoglycans (GAG) favored the aggregation of the Aβ peptide. This effect is inhibited by Alzhemed™, and studies have shown that the compound

blocks the fibrillation of the Aβ peptide *in vitro* and in the brain of transgenic mice. This substance is administered orally, is well tolerated, is non toxic and possesses a good bioavailability in the brain. The plasma levels of Aβ 42 fall according to the dose in the course of a three-month treatment, and the cognitive state is stabilized in the case of patients with a moderate form of Alzheimer's disease. Alzhemed™ is one of the most advanced candidates among the current "anti-amyloid" strategies, since it is in phase III at the present time.

Current state of progress regarding different therapeutic strategies

Stage	Therapeutic strategy	Mechanism targeted
Abandoned	Active immunotherapy: AN-1792	Intact anti-Aβ vaccine
Preclinical	Inhibition/blocking of β- and -γ-secretase Activation of α-secretase: Bryostatin 1 Kinase inhibitor	Reduction of Aβ production Activation of Kinase protein C Neuroprotection/Reduce neurofibrillary degeneration
Phase I	Inhibition/blocking of γ-secretase	Reduction of Aβ production
Phases I, II and III	Passive immunotherapy	Monoclonal antibody against Aβ
Phases I and II	Active immunotherapy Kinase inhibitor	Anti-fragment Aβ vaccine coupled with a hapten Neuroprotection/Reduce neurofibrillary degeneration
Phase II	Chelation of heavy metals: Clioquinol derivative	Chelation of copper and zinc to reduce the aggregation of Aβ
Phase III	Anti-polymerization: Tramiprosate (Alzhemed™) Modulators of γ-secretase: R-Flurbiprofen NSAID Estrogens, NSAID, antioxidants, statins	Glycosaminoglycan mimetic Reduction of Aβ Reduction of Aβ 42 production Neuroprotection

Numerous studies suggest that oxidative stress comes into play before the onset of the symptoms of Alzheimer's disease, and various antioxidant strategies have thus been developed. However, the studies have given rise to at times contradictory results and have not been followed up by clinical trials at the present time.

It has been shown that Alzheimer's disease is associated with a neuronal loss and an alteration of the synaptic architecture, and it is well known that the neurotrophic factors provide protection against neuronal death and amyloid toxicity. The NGF (Nerve Growth Factor) is principally targeted at cholinergic transmission. The first study of NGF application *ex vivo* in 8 patients with a moderate Alzheimer's disease established an absence of toxicity at 22 months, and an improvement in the evolution of cognitive decline. These initial results on a gene therapy approach are encouraging but await confirmation on larger cohorts. It is unlikely that a strategy focusing solely on cholinergic transmission can "cure" Alzheimer's disease but it may turn out to be complementary to the anti-amyloidergic approaches, particularly in the early or moderate stages of the disease.

Estrogens are pleiotropic hormones that could be implicated in the neuroprotection processes. However, at the present time it is not possible, on the strength of the studies carried out, to point to a significant effect of the estrogens on the formation of the Aβ peptide.

We do not yet fully understand the mechanisms by which cholesterol increases the Aβ peptide levels. Studies would seem to show that it negatively regulates the α-secretase activity and potentiates the β- and γ-secretase activity. However, the beneficial role of the

statins has recently been called into doubt: no significant effect on the cognitive functions has been established.

In transfected cells or in "Alzheimerised" transgenic animals, certain NSAIDs[1] (ibuprofen, indomethacin) can reduce the production of Aβ 42. Several controlled therapeutic trials have been conducted but there is no consensus as to their conclusions.

Research on Alzheimer's disease today makes use of animal models where the pathology principally affects the hippocampus and the cognitive functions, as is the case in the human pathology, and such models help to give us a better understanding of the aggregation mechanisms of the tau proteins and to envisage a therapeutic strategy.

The abnormal phosphorylation of tau proteins results in a disruption of microtubule stability and a loss of axonal transport. Molecules stabilizing the microtubules (taxol derivatives) have therefore been proposed in the treatment of tauopathies. Their use in a clinical situation is, however, highly unlikely in view of the fact that these substances are not specific to neurons. Moreover, certain tauopathies present an overexpression of tau 4R proteins facilitating the stability of the microtubules, and taxol will probably show the same adverse effects.

The abnormal phosphorylation of the tau proteins would appear to favor their aggregation in filaments. The use of kinase inhibitors thus holds out promise, with lithium or GSK3β inhibitors being used to slow down the progress of neurofibrillary degeneration. This approach is currently being tested in therapeutic trials. Similar results have been obtained for MAP kinase inhibitors. Similarly, an understanding of the role played by phosphatases and prolylisomerases is equally crucial for regulating the dephosphorylation mechanisms.

While phosphorylation is considered as a major event of tau protein aggregation, other post-translational or conformational modifications are also suspected. In addition, the interactions between tau proteins can lead us to consider the development of intercalating agents inhibiting their aggregation. It has recently become possible to follow the aggregation of the proteins directly in spectroscopy by nuclear magnetic resonance (NMR) and to identify the peptidic sequences implicated. This body of work allows to identify intercalating agents and opens up new therapeutic perspectives for tauopathies.

Thanks to the progress made in the understanding of the biological mechanisms (with the highlighting of the factors implicated in the etiopathogenesis of Alzheimer's disease), biological markers have been identified: total tau proteins, hyperphosphorylated tau proteins and the Aβ 1-42 peptide. These markers, measured in the cerebrospinal fluid, are explored in the context of research programs conducted in expert centres or networks of specialists. Simultaneous measurement techniques are currently under development. According to a study carried out in 2006, the combined alteration of the three markers would make it possible to identify patients likely to evolve from an MCI towards Alzheimer's disease. Other biological candidates are now emerging, such as truncated forms of Aβ peptides, enzymes implicated in the metabolism of the precursor APP or in the metabolism of the tau protein, and proteins associated with the lesions of Alzheimer's disease. The possibility of taking biomarker blood levels would be an important step forward and would give fresh impetus to the study of their application in common clinical practice as a complement to clinical examinations.

[1] Non Steroid Anti-Inflammatory Drugs

The neuropsychological approach is of fundamental importance in the evaluation of cognitive disorders

Over the last twenty years, developments in cognitive neuropsychology and clinical research, a growing awareness of the public health problem represented by Alzheimer's disease and the establishment of diagnostic criteria, have combined to secure considerable progress in the description of the cognitive disturbances relating to this pathology. In view of the precocity and extent of these disturbances, the neuropsychological examination[1] is a priority in diagnosing Alzheimer's disease. This examination highlights and characterizes the disorders, and differentiates them from those occurring in the other neurodegenerative diseases, or in the depressive syndrome, as well as in the age-induced decline of certain cognitive capacities. Lastly, the neuropsychological check-up plays an important part in revealing those capacities which have been preserved and which can serve as the basis for non-pharmacological therapies.

Although it has been shown that the onset of the disease can take several forms, the first signs are usually related to memory disorders. The memory comprises several components – or memory systems – which are not affected in the same way. Episodic memory stores memories of personally-experienced events, situated in the temporal spatial context of their acquisition. Disorders of episodic memory are central to Alzheimer's disease and are characterized by difficulties in acquiring new information and in retrieving memories, particularly those relating to recent events. Such disorders are to be distinguished from the decline in memory linked to increasing age, both in degree and kind, since they concern the different stages of memorization: encoding, storage and retrieval of information (retrieval disorders are less specific since they are observed in numerous diseases). Isolated disorders of episodic memory are characteristic of amnesic MCI. Most of the patients show impaired scores in tests of episodic memory: learning of lists of words (whether or not linked semantically), primacy effect (remembering the first words in the list), recognition of words and remembering a story or a geometrical figure. The most sensitive and at the same time the most specific measurement would appear to be the delayed recall of a list of semantically related words. This might be explained by the patients' difficulty in organizing the items to be memorized by semantic categories.

Episodic memory is usually examined by means of tasks of learning words or remembering stories. One test in particular is now commonly used in memory consultations: "16-item free and cued selective reminding test", derived from Grober and Buschke's procedure. The test sets out to differentiate episodic memory "genuine" disorders from "apparent" disorders linked, for example, to the use of ineffective strategies or to attention disorders having repercussions on memory performance. In Alzheimer's disease, there is a deficit in the free recall of information, and there is scarcely any improvement in performance with cued remembering (e.g. "What was the name of the flower?"). This points to difficulties in encoding and storing information.

Semantic memory, which stores words, concepts, knowledge about the world as well as personal semantics (general knowledge about oneself), may be disrupted in early Alzheimer's disease, while it stands up very well to the effects of age, thus arguing in favor of a degenerative disease. Disturbances of semantic memory have regularly been highlighted

[1] The different tools mentioned are commonly used by clinical psychologists trained in neuropsychology when testing a patient consulting for suspected Alzheimer's disease, or when evaluating the evolution of cognitive deficits in the case of mild to moderate illness. Other tools are available to doctors wishing to evaluate the severity of a diagnosed dementia or for diagnosing a patient presenting clear cognitive disorders (see diagnostic procedure).

in MCI patient groups and would appear to be among the best predictive indices of subsequent cognitive decline.

Semantic memory disorders can be revealed through questionnaires focusing on knowledge of concepts or famous persons. The disorders have a greater impact on specific knowledge than on general knowledge and are expressed by constant errors from one moment to another and from one test to another, thus testifying to the deterioration of the concepts. These difficulties are not to be confused with disorders of semantic memory access which are characterized by difficulties in producing the right word, but without loss of concept. Here, it is a case of language disorders, which are very frequent in Alzheimer's disease and are revealed by means of image denomination or lexical evocation tests. The written language is also disturbed in Alzheimer's disease, the most telltale symptom being a tendency to even out the writing of irregular words.

Working memory, by which small quantities of information are stored and manipulated for a limited lapse of time, is also disturbed at a very early stage of Alzheimer's disease. The "central executive", which is responsible for the allocation of attention resources and the coordination of the other working memory subsystems, is particularly sensitive to the disease. Working memory is commonly evaluated through attention span tasks (repetition of series of figures, in the right order and back to front) or dual-task paradigms. The impairment of the central executive should be considered as one of the fundamental cognitive disturbances of Alzheimer's disease with repercussions on multiple tasks.

To sum up, Alzheimer's disease affects first of all episodic memory, semantic memory and working memory, the three most elaborate memory systems. On the other hand, lower-level systems, such as the perceptual representation system (underpinning perceptual priming effects) and procedural memory (underpinning habits), show more resistance, at least during the early stages of the disease. The preservation of these memory systems may serve as a base for non-pharmacological therapies of patients.

Other cognitive functions, in addition to memory and language, are impaired in Alzheimer's disease, particularly the executive functions, or high-level mental processes implicated in the accomplishment of a purposeful activity. Disruption often occurs early on and can appear at a pre-dementia stage. The identification of executive disorders is an important challenge given their repercussions for the patient not only in his everyday life but also in becoming aware of his cognitive deficit. The Wisconsin Card Sorting Test has proved effective but it has the drawback of being "multi-determined", which explains why simpler tasks are sometimes preferred. Such tests involve "basic" executive functions such as mental flexibility and inhibition capacity (respectively the Trail Making Test and the Stroop Test).

Lastly, other disorders appear at a fairly early stage of Alzheimer's disease: apraxia (difficulty in executing coordinated movements), agnosia (difficulty in identifying objects) or visuospatial disorders expressed by difficulties in producing (spontaneously or by copying) geometrical or figurative drawings. One of the most frequently used tests is the Rey complex geometrical figure test.

In short, the work carried out on Alzheimer's disease in recent years has resulted in a precise description of the cognitive disturbances and their cerebral substrates. These disturbances are above all characterized by disorders of the various memory systems. The studies also dwell on those capacities which resist over longer periods of time. Some of the most recent work seeks to identify the earliest disorders by studying "pure" amnestic MCI patients. Although these cases are rare, a study of such patients, and particularly those who subsequently develop Alzheimer's disease - "converters"), has had the merit of driving home the need to look out for, in patients liable to present with Alzheimer's disease, "genuine" disorders of the episodic memory, especially in delayed recall, an alteration of the semantic

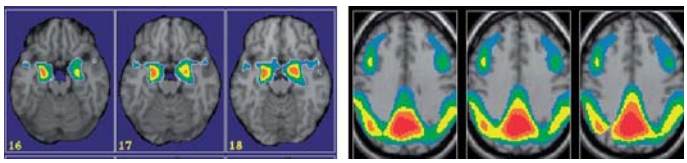
memory, executive functions or visuospatial abilities. This body of knowledge should yield an earlier diagnosis of the disease and thus secure better care and treatment of patients.

Cerebral imaging provides knowledge on structural anomalies and functional alterations

Magnetic resonance imaging (MRI) studies have shown cerebral morphological alterations associated with Alzheimer's disease and concerning first of all the hippocampal region, in line with the regional distribution of neurofibrillary tangles. Numerous authors have demonstrated a marked atrophy of the medial region of the temporal lobe compared to healthy old subjects, even at a pre-dementia stage of the disease. The atrophy then spreads to other areas (external temporal cortex, posterior cingular gyrus, temporoparietal cortex), in line with the expansion of the neurofibrillary degeneration.

Alzheimer's disease causes a demyelination and axonal loss affecting the white matter connecting the associative cortices (corpus callosum, white matter of the temporal, frontal and parietal lobes) and the white matter of the limbic system. The atrophy of the internal temporal area, characteristic of Alzheimer's disease, is also accompanied by a vulnerability of the hippocampal and parahippocampal fibers. These anomalies are easier to identify by diffusion tensor MRI than by standard anatomic MRI.

Functional imaging studies using positron emission tomography (PET) show that the reduction in the metabolism of the posterior cingular gyrus constitutes the earliest anomaly, since it is also present in patients suffering from MCI and in healthy subjects carrying the *APOE4* gene (presenting a higher risk of developing Alzheimer's disease). The early functional damage of this area (little affected by atrophy) could at least partly be explained by the remote effect of the morphological alteration of the hippocampal region. At a more advanced stage of the disease, the fall in metabolism extends to the temporoparietal cortex and the frontal cortex, but the metabolism of the primary motor and sensory cortices, basal ganglia and cerebellum remains relatively unscathed. However, somewhat unexpectedly, the hippocampal region does not often appear to be hypometabolic (including in large samples of patients). This difficulty in identifying a significant hypometabolism in the hippocampus in Alzheimer's disease has sometimes been attributed to methodological issues, but even in the best conditions, a reduction in the metabolism is significantly less important than in the posterior neocortical regions. This suggests the existence of compensatory mechanisms (the exact nature of which has yet to be determined) that could be positioned in the hippocampus, even before the disease becomes evident.



Structural abnormalities detected by MRI (left) and functional abnormalities in PET (right) in Alzheimer's disease: the colored zones represent the significant differences between the patient group and the control group (data from Inserm Unit U 923, Caen)

Thus, the structural and functional abnormalities are not perfectly superimposed, the former concerning first of all the hippocampal region and the latter the posterior cingular gyrus. This difference is particularly striking in MCI patients for whom studies have also emphasized early functional abnormalities of the temporoparietal cortex, which appear to be

specific to patients who will subsequently develop Alzheimer's disease, according to current diagnostic criteria.

The way the cerebral alterations are distributed allows to explain cognitive disabilities, particularly episodic memory disorders, in Alzheimer's disease. This has been established by means of the method of cognitivo-metabolic or cognitivo-morphological correlations, or by the activation method. The first of these methods, consisting of establishing links between cognitive disorders and metabolic deficits or grey matter atrophies, has shown that the dysfunctions of the hippocampal region and the posterior cingular cortex underlie the encoding and retrieval disorders respectively. This method also identifies the areas involved in the compensatory mechanisms, at a stage when the structures normally involved in episodic memory no longer make it possible to underpin the patients' residual performance.

PET or functional MRI activation studies carried out in Alzheimer's disease patients converge towards a reduction of hippocampal activations, both during encoding and retrieval, and often show an increase of the activations situated in the associative cortex, in particular the frontal cortex. The notion of compensatory mechanisms is often advanced as an explanation for this last result, and indeed this hypothesis has recently been reinforced by significant correlations found between frontal activations and memory performance. The compensatory mechanisms would appear to be underpinned by the hippocampus in MCI patients, and in fact, these patients have greater hippocampal activations than healthy subjects.

New imaging methods are now being developed in order to visualize senile plaques and neurofibrillary tangles, as well as to understand the connectivity disorders between regions and white matter abnormalities, but there are no immediate applications at clinical level. Similarly, in the context of research, functional brain imaging is of precious value for gaining a better understanding of the pathophysiology of Alzheimer's disease. It is a powerful tool in terms of early diagnosis and prediction of cognitive decline. For a variety of reasons (cost, availability, variability from one individual to another), this technique cannot be used as a matter of routine, and the easiest technique to adopt in clinical practice turns out to be MRI morphological imaging. It is set to make an even greater contribution with the automation of image processing techniques making it possible to view cerebral atrophy in areas playing a crucial role in the onset of cognitive impairment. In situations where this technique is contraindicated (pace maker, claustrophobia, etc.), a scanner can be useful with patients who are not eligible for MRI.

The clinical diagnosis is not usually pronounced until the confirmed dementia stage

At the present time, Alzheimer's disease is clinically defined as a dementia whose diagnosis is founded on the presence of a cognitive decline with repercussions on everyday life. Thus, the diagnosis is based on a two-stage approach: firstly, the demonstration of a dementia syndrome and then, secondly, the identification of elements arguing in favor of Alzheimer's disease (slow and insidious encroachment of cognitive disorders).

The disease was long considered a degenerative disorder of the period preceding old age (before the age of 65). The cognitive and behavioral disorders observed in the elderly were then grouped under the term "senile dementia". It was not until the 1960s that the uniqueness of Alzheimer's disease, the most frequent cause of dementia, was recognized irrespective of the age at which it began. Many criteria for the diagnosis of Alzheimer's disease have been put forward, chief among them being ICD-10 (World Health Organization,

1993), DSM-IV (*American Psychiatric Association*, 1994) and NINCDS-ADRDA (*National Institute of Neurological and Communicative Diseases and Stroke/Alzheimer's Disease and Related Disorders Association*, 1984) (Appendix 2). All refer to a gradual impairment of memory and other cognitive functions in the absence of any other disease that could account for the emergence of a dementia syndrome. The sensitivity of these criteria is globally satisfactory (an average of 80% over all the studies), but there is a lesser specificity (around 70%) for the diagnosis of probable Alzheimer's disease with post-mortem confirmation.

The use of diagnostic criteria for Alzheimer's disease was the subject of recommendations by the National Agency for Accreditation and Evaluation in Health – *Agence nationale d'accréditation et d'évaluation en santé* (Anaes, 2000). Anaes (now the French National Authority for Health – *Haute autorité de santé* (HAS)) in particular recommends a specialist opinion with a neuropsychological assessment and brain imaging. European guidelines were drawn up in 2006 and emphasize the importance of evaluating cognitive functions, with a global measurement of the cognitive function, an assessment of memory, the executive functions and the instrumental functions (language, reading, writing, praxia, etc.). Finally, the evaluation of functional activities of daily life is a fundamental element of the dementia syndrome. Generally speaking, the diagnosis of Alzheimer's disease is particularly difficult at the beginning and end of the development of the disease. At the outset, the symptoms are discreet and may be masked or confused with difficulties related to the normal ageing process. At the end of the evolution, at the final stages of cognitive and behavioral degeneration, it is difficult to find, from examination, specific marks of a disease. This being the case, it is all the more important, in the diagnosis of Alzheimer's disease, to question the patient's family circle about the manner in which the disorders emerged.

Alzheimer's disease remains under-diagnosed in France. According to the available epidemiological data, only half of the patients suffering from the disease are currently identified. There are several reasons for this under-diagnosis, in particular the fact that many doctors are not yet convinced of the benefits of a medicalised approach to Alzheimer's disease or its therapeutic treatment. This under-diagnosis is chiefly observed in elderly patients, but it also concerns younger subjects. When the diagnosis is eventually made, it is often lately, typically at the stage of confirmed dementia.

Once the diagnosis has been established, it will have to be announced to the patient and will now govern everything that follows: the treatment and health care plan, a better attitude on the part of the patient's family circle, anticipation of periods of crisis and the choice of decisions in which the patient can participate.

As we improve our knowledge of the condition, and as new paraclinical tools are developed in the field of neuro-imaging and biomarkers, the likelihood is that Alzheimer's disease, currently inseparable from the MCI syndrome, will be diagnosed at earlier stages in the future.

A diagnosis at the pre-dementia phase of the disease could become possible

In Alzheimer's disease, the first cerebral lesions are present several years and even several decades before the first symptoms appear. This long pre-symptomatic phase, during which the lesions gradually and surreptitiously take form, is followed by a transitional phase in which the symptoms appear but without reaching the dementia criteria as set out in current classifications (ICD-10, DSM-IV, NINCDS-ADRDA). Over the last few decades, various authors have endeavored to pin down this first symptomatic phase of Alzheimer's disease by identifying patients suffering from memory disorders (or other cognitive disorders)

which are not sufficiently severe to have an impact on social and occupational activities or to alter autonomy. These studies have shown that, compared to other subjects of the same age but without cognitive disorders, such patients were at greater risk of developing a dementia syndrome after one or more years of follow-up.

The condition of these patients is currently defined as a mild cognitive impairment (MCI). MCI criteria have evolved over the past fifteen years. Among those proposed and clarified on several occasions: a complaint relating to memory (backed up by the patient's family circle and friends), a confirmed memory deficit, a globally normal cognitive functioning, preserved everyday basic activities and the absence of dementia. Several forms of MCI have recently been singled out: pure amnesic MCI, MCI involving several cognitive domains, excluding memory, MCI characterized by a deficiency in one particular area, not including memory. The aim is to predict as well as possible the pathology lying behind the observed disorders. Having been a very general syndrome, the various MCI categories are much better defined today.

In MCI, the presence of an episodic amnesic syndrome is significantly associated with an evolution towards Alzheimer's disease. Certain authors criticize the concept of MCI (despite its subsequent subdivisions) on the grounds of its heterogeneity and feel that the time has come to explore the possibility of identifying patients suffering from Alzheimer's disease at the pre-dementia stage, on the basis of verified memory disorders and neuroimaging or biomarker data, bypassing the syndromic stage of MCI. New criteria are currently being studied with a view to establishing a diagnosis of probable Alzheimer's disease before the dementia threshold (Appendix 2).

Cognitive decline is accompanied by psychological and behavioral symptoms

Alzheimer's disease is not just a question of cognitive disorders. On the contrary, as the disease evolves, most difficulties will probably be caused by the associated non-cognitive symptoms. It should be noted that most behavioral disorders are related with a confusional syndrome, a pain, an iatrogenic effect or a poorly adapted environment, still inadequately taken into account due to a lack of training for family helpers and health care professionals.

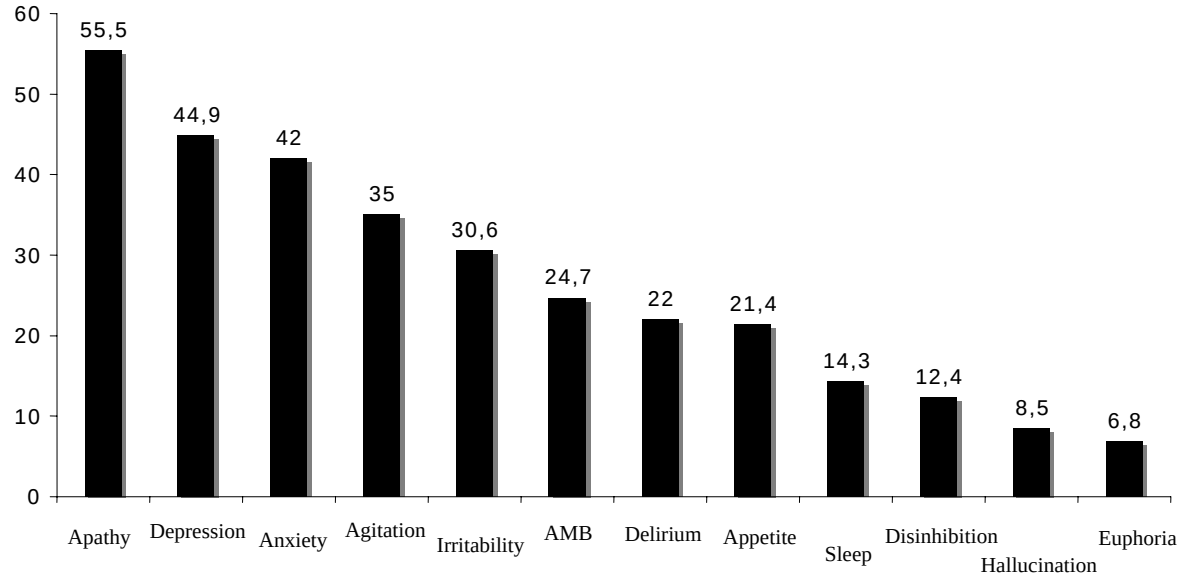
The neuropsychiatric, psychological and behavioral symptoms of dementia form part of the clinical picture of Alzheimer's disease. They are defined as primary manifestations of cerebral dysfunction, and appear specifically as a result of damage to a system or circuit such as the limbic system or the cortico-subcortical circuits. Neurodegenerative diseases such as Alzheimer's disease produce both structural and chemical alterations, and the neuropsychiatric symptoms can be influenced by one or other of these alterations.

However, it should be pointed out that these specific biological modifications, while necessary, are not in themselves sufficient to produce the neuropsychiatric symptoms, for other factors of a psychological and social nature are also at play in determining which patient will manifest behavioral modifications.

Irrespective of the severity of the disease, the most frequently encountered symptom is apathy followed by depressive symptoms and anxiety. A syndromic grouping (affective symptoms, apathy, hyperactivity, psychotic symptoms) is useful for an understanding of their etiology and for improved treatment and care.

According to recent data, a history of depressive disorders would seem to be considered as a risk factor of Alzheimer's disease. In the pre-dementia phase of the disease, apathy is the

earliest neuropsychiatric symptom. At the dementia stage, numerous symptoms are present in over 80% of patients, as emphasized by various European studies.



Frequency (%) of psychological and behavioral symptoms evaluated with the Neuropsychiatric Inventory (NPI) in Alzheimer's disease (European studies)

AMB: Aberrant Motor Behavior

The evaluation of neuropsychiatric, psychological and behavioral symptoms of dementia, using specific tools, is indispensable not only at the time of screening but also at diagnosis and during the evolution of the disease.

This evaluation must fulfill various conditions:

- As a complement to the reference instrument, the Neuropsychiatric Inventory (NPI), instruments focused on the evaluation of a specific dimension must be used (apathy, early-stage depression, agitation, hyperactivity, psychosis (moderate-to-severe stages)
- The reference evaluation is of course that of the person accompanying the patient, but the point of view of the patient and the clinician must also be taken into account
- The clinician's evaluation must take the answers to the standardized questionnaires into account, but also the direct observation of the patient's behavior in the course of the clinical situations (consultation, outpatient hospitalization, taking of neuropsychological tests)
- In order to ensure that the evaluation is as objective as possible, the precise record of the frequency of the disorders must be separated from the evaluation of gravity
- The evaluation must be accompanied by a search for somatic causes or an iatrogenicity that could at least partially explain the onset of the disorders
- Finally, the evaluation must assess the impact on autonomy and everyday activities

In most cases, the evaluation is conducted in the form of an interview with a person who accompanies the patient and who is aware of his/her behavior. A patient's self-evaluation is less often used.

The psychological and behavioral symptoms have consequences on the development and lifestyle of the patient (more frequent stays in institutions) and also on the intensity of the

burden felt by the accompanying person. This means that the dynamics between the patient and the accompanying person should always be taken into account when evaluating these symptoms.

Loss of weight, balance disorders and other deficiencies are also associated with the disease

Between 20% and 40% of patients suffering from mild to moderate forms of Alzheimer's disease are affected by weight loss, irrespective of where they live. This weight loss increases as the disease develops and represents a predictive factor of mortality. Certain studies also show that loss of weight can precede the diagnosis of the disease. In this case, it could be one of the early signs of the pathological process.

Clinical practice shows that weight loss is accompanied by a series of complications (alterations of the immune system, muscular atrophy, falls, fractures, dependence, etc.) leading to a worsening of the patient's health and to an increased risk of institutionalization and mortality.

Weight measurement must therefore be one of the follow-up parameters for patients suffering from Alzheimer's disease. In fact, it is possible, with adequate treatment and care, to reverse the nutritional status, particularly if it is detected at an early stage.

The disease may be associated with the occurrence of eating disorders reducing energy intake. Such disorders may include anorexia, a refusal to eat or praxic difficulties. A somatic or iatrogenic cause should systematically be sought. Lack or decreased sense of smell (anosmia), common in Alzheimer's disease, may also have an impact on dietary intake. Weight loss is always a sign of an insufficient calorie intake which must therefore be adjusted on an individual basis. Most studies show a significant weight recovery with increased dietary intake, particularly by means of oral supplements. Other authors have shown that the nutritional management of patients thanks to dietary training dispensed to family helpers could also have a positive impact. Finally, physical activity is a simple way of helping to stimulate appetite and to restore a patient's energy balance.

Given the importance of this phenomenon in Alzheimer's disease, screening for under-nourishment should form part of the patient's initial evaluation and follow-up.

Gait and balance disorders as well as falls are present in the course of Alzheimer's disease. It would even seem that motor performance is affected from the early to moderate stages of the pathology. The diagnosis of Alzheimer's disease increases the risk of falling threefold, irrespective of the stage of the disease and the intake of medicine. Many factors contribute to the worsening of gait disorders and to the risk of falls in the mentally ill: behavioral disorders, malnutrition and the associated sarcopenia, as well as iatrogenic causes, particularly the intake of neuroleptics. The occurrence of falls is also rendered more likely by judgment disorders, attention disorders (especially in the presence of several simultaneous items of information) and visuospatial difficulties. Alzheimer's disease may also be associated with a change of visual perception irrespective of any ophthalmological condition. Thus, perception of shapes, movements and colors may be altered.

As with the aggravation of cognitive disorders, balance disorders are an independent predictor of loss of autonomy, and the treatment of such disorders should be considered and assessed.

Various mechanisms may be at the origin of these disorders, some of them responding to damage of the subcortical motor circuits, and others to damage of cortical cognitive functions (apraxia and executive disorders).

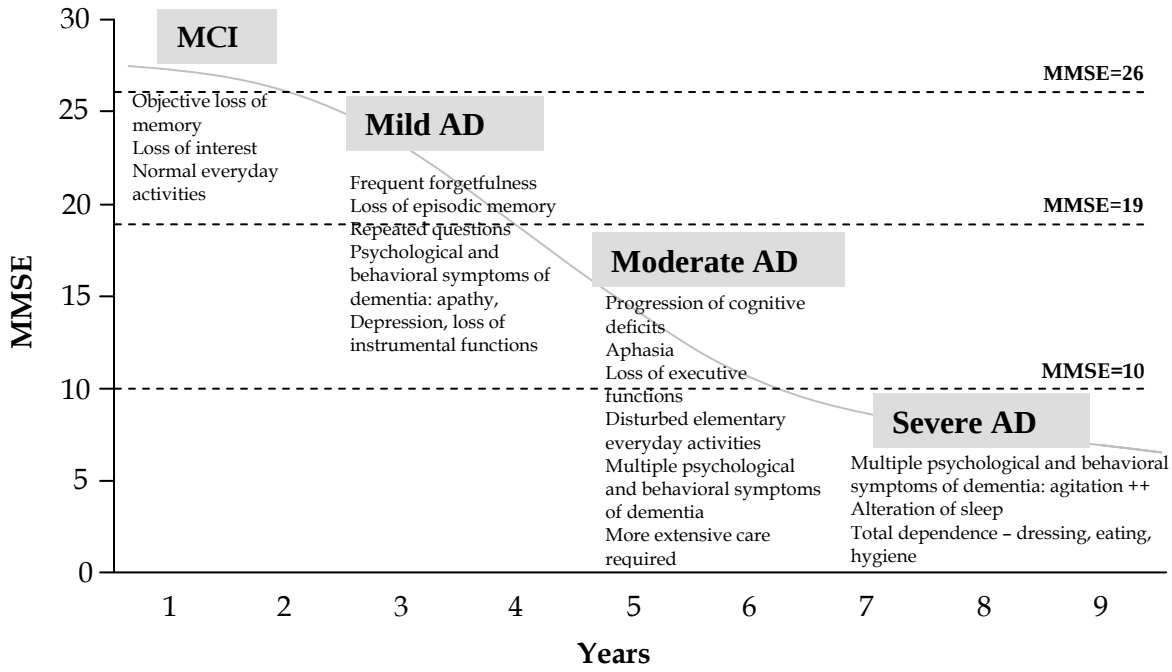
Persons suffering from Alzheimer's disease are three times more likely to have a fracture than the general population, even allowing for age and sex. Falls are generally more severe in patients with Alzheimer's disease. It has been shown that these patients had a higher incidence of fracture of the hip than control populations of the same age; and this type of fracture usually has a worse functional prognosis when the subject suffers from Alzheimer's disease. Apart from fractures, falls also have functional or social repercussions: psychomotor inhibition, swifter functional decline, physical deconditioning and commitment to an institution.

Automatic reflexes (palm-chin, grasping, pouting, sucking reflexes, etc.) reappear and their presence is linked to the occurrence of incontinence. It would seem that 50% of patients are incontinent after 6 years and 80% after 8 years. Incontinence must always be the cue for a search for a potentially reversible cause, particularly in the absence of automatic reflexes. Blood pressure tends to drop, especially in the case of severe dementia.

The risk of convulsive attacks is multiplied by 10 in patients suffering from Alzheimer's disease, as with other cases of dementia. These attacks are reported in 21% of institutionalized patients suffering from Alzheimer's disease, and 10-20% of cases submitted to autopsy, climbing as high as 64%. This would seem to be a factor of cognitive decline. Myoclonus frequency varies from 0 to 80% and increases in line with the severity of the disease. It is sometimes an important feature of the neurological examination of early-starting "family" forms of the disease.

The disease evolves from cognitive decline to loss of autonomy and then dependence

Cognitive decline measured by the MMSE (Mini Mental State Examination) is not linear over time. It seems to advance more slowly during the mild and severe stages of the disease and faster at the moderate stages. The rate of the initial decline predicts the subsequent (fast or slow) decline. The severity of the initial cognitive decline (at the time of the first visit) is, logically enough, a frequently found factor of poor prognosis. On the other hand, a measurement remaining stable for at least 2 years ("plateau") is a good prognosis factor over a 7-year period of follow-up. However, cognitive decline varies from one individual to another. A patient losing 3 or more points on the MMSE per year is considered as a "rapid decliner" while a "slow decliner" is one who loses less than 2 points per year on the same examination. A better prognosis would seem to be the form of the disease in which memory disorders predominate (temporal form) with few or no executive function disorders. Poor prognosis factors have also been identified: male sex, apraxia and "parietal" signs, language disorders (not confirmed by certain studies), signs of frontal impairment, little cranium, psychotic and Parkinsonian symptoms, even in patients who have never received neuroleptics.



Progression of the symptoms of Alzheimer's disease (from Feldman and Woodward, 2005)

MMSE: Mini Mental State Examination; MCI: Mild Cognitive Impairment; AD: Alzheimer's disease

Different scales for evaluating the evolution of decline

Scales for measuring general cognitive deterioration used for follow-up of Alzheimer's disease

Type of scale	Reference
Mini Mental State Examination (MMSE)	Folstein et coll., 1975
Alzheimer's disease Assessment Scale: cognitive subscale (ADAS-Cog)	Osen et coll., 1984
Mattis Dementia Rating Scale	Mattis, 1976

The *Mini Mental State Examination* was elaborated in 1975 by Folstein and colleagues as a simple standardized test for evaluating the cognitive performance of subjects, and where appropriate to quantify their deficit. This short test consists of 30 items.

The faster decline and greater mortality in the male population could be explained by the co-existence of more numerous pathologies and therapeutic prescriptions, particularly the intake of anticholinergics, and the associated vascular pathology. However, the vascular risk factors do not influence the progression of Alzheimer's disease at 18 months or on the passage from the mild to the moderate stage at 3 years. But high blood pressure in patients under the age of 65 years, and the fall in functionality of the cerebral microvessels measured by transcranial Doppler could have an influence on cognitive decline.

The alteration of the cognitive functions is a risk factor for the onset of disabilities for basic everyday activities. The score of 16 on the MMSE seems to mark a transition point below which disruptions of basic everyday activities begin to emerge within 12 months. Dependence corresponds to the partial or total impossibility for a person to perform everyday activities unassisted, while autonomy can be defined by the person's ability to fend for himself.

The disabilities are evaluated by scales measuring the ability to carry out various everyday activities. The Instrumental Activities of Daily Living Scale (IADL) and the basic Activities of Daily Living Scale (ADL) are among the most commonly used scales.

Many studies show that the decrease in daily activities in Alzheimer's disease is present from the very early stages, affecting social life and leisure activities very early on. Indeed, the reduction in social activities is one of the first signs arousing the attention of the patient's family circle in the same way as memory difficulties; it is closely associated with apathy, diminished motivation and difficulties in planning ahead. Other studies show that even at the stage of MCI, some people may already suffer from an inability to perform certain tasks of everyday life. When followed up, these subjects showed a significantly higher risk of an evolution towards dementia compared to those free from such disabilities.

The reduction of everyday activities is a key element in the diagnosis of "dementia". For many elderly persons, the emergence of dependence in their everyday activities signals the start of the downward spiral of fragility leading to the need for formal and informal assistance, with frequent hospitalizations and stays in retirement homes. Most of the studies show the negative impact of dependence on the quality of life of persons suffering from Alzheimer's disease. It should, however, be borne in mind that there is a considerable variation in the worsening of dependence over time in patients. Indeed, although the evolution of the change in cognitive functions is a determining factor, other factors also come into play, such as cardiovascular pathologies, rheumatologic conditions and sensory deficits.

Most commonly used scales for global clinical follow-up and dependence in Alzheimer's disease

Type of scale	Reference
Global clinical evaluation scales	
Clinical Dementia Rating scale (CDR)	Morris, 1993
Global Deterioration Scale (GDS)	Reisberg et coll., 1982
Dependence evaluation scales	
Instrumental Activities of Daily Living (IADL)	Lawton and Brody, 1969
Activities of Daily Living (ADL)	Katz et coll., 1963
Disability Assessment for Dementia (DAD)	Gélinas et coll., 1999
AGGIR grill (Gerontological Autonomy – Iso-Resources Group)	Website*
Global Deterioration Scale-Functional Assessment Staging	Auer and Reisberg, 1997
Progressive Disease Scale	DeJong et coll, 1989
Alzheimer Disease Cooperative Study-Activities of Daily Living (ADCS-ADL)	Galasko et coll, 1997
of Daily Living (ADCS-ADL)	
Physical Self-Maintenance Scale	Lawton and Brody, 1969
Functional Rating Scale	Crockett et coll, 1989

* http://vosdroits.service-public.fr/particuliers/F1229.xhtml

The different data highlight the complementary nature of the gerontological functional approach and the standard neurological approach in the screening and follow-up of patients suffering from or at high risk of dementia. They also show the important part played by the evaluation of functional deficits and handicaps in drawing up the health care plan. Indeed, it is essential to be in a position to evaluate the impact of the different functional or cognitive deficits on daily life. The effect will be generally discussed in terms of "risks", which will differ depending on the stage of the disease: driving a car, financial autonomy and keeping a budget, the patient's adaptation to his lifestyle at home, etc. Life expectancy is impaired by Alzheimer's disease, regardless of the stage of dementia. The mortality of dementia patients is doubled in patients above the age of 85 years compared to subjects not suffering from dementia. Mortality is closely linked to the gradient of cognitive decline. There is little

information on survival in the case of presenile dementia (occurring before the age of 65 years).

Most studies point to age and the male sex as being higher predictive factors of mortality. The median survival time varies from 8.3 years in persons diagnosed with Alzheimer's disease at the age of 65 years, to 3.4 years for those diagnosed at the age of 90 years.

Life expectancy has increased over the past fifteen years, probably due to better care, even though dementia patients are still treated less well than others. The causes of death of patients with Alzheimer's disease are mainly pneumopathy disorders, cardiovascular disorders including pulmonary embolism, and cerebral vascular accidents. The risk of death from a cerebrovascular accident is multiplied by 3.7.

Patients suffering from Alzheimer's disease are at greater risk of being committed to an institution than those free from dementia. This risk is linked to cognitive decline, age, educational level, sometimes to marital status, but gender plays little part. Behavioral disorders, particularly agitation, are also associated with institutionalization.

The caregiver's burden (as measured by the Zarit Burden Interview) and the lifestyle (at home with a member of the family other than the spouse, or alone) are independent factors governing entry into an institution at 1 year. Patients whose caregivers are spouses are less at risk of entering an institution than the others. An Australian study has shown that, in the 5 years following the diagnosis of dementia, 76% of the patients were institutionalized and 42% had died. These figures were considerably reduced when information and support were forthcoming for the patient's family circle. The more a caregiver living with the patient has a good evaluation of his quality of life and returns a low score on the "burden" test, the less likely it is that the patient will be committed to an institution. This drives home the importance of giving direct help to the caregiver.

In patients at an advanced stage of dementia, mortality at 6 months after entering an institution varies from 28 to 35%. The later the patients enter the institution, the less institutionalization will shorten their survival. Alzheimer's disease can affect young people, aged under 65 or even 50 years in some sporadic forms, and even younger subjects in certain "family" forms. Typically, young patients are more aware of their disorders and are more affected than older subjects. They often have attention difficulties and a working memory deficit (both proportionately more severe than their episodic memory disorders), and instrumental disorders, in particular with regard to language and praxis. Their scores on depression scales while the disease is developing undergo more changes than those suffering from late-developing forms of the disease. Their scores on neuropsychological scales decline at a faster rate. Pneumonia is the leading cause of death, as with the elderly, whereas it is not the most usual cause of death for people of this age.

Patients suffering from dementia are on the whole less well treated from the medical point of view than those free from dementia. There are, for example, fewer instances of cardiovascular disease or cancer in the death certificates of patients suffering from Alzheimer's disease than in the general population – a sure sign that such conditions are less often diagnosed. Similarly, hypercholesterolemia and hypothyroidism are less often diagnosed in patients with dementia. The exact cause of death is specified in only half of the autopsies performed.

There is no curative treatment for the disease at the present time

From the medicinal point of view, Alzheimer's disease is currently treated symptomatically (and not curatively).

Two classes of medicinal drugs are available. The first class acts on the acetylcholine deficit observed in the patients' brain. It is made up of three molecules: donepezil[2], rivastigmine[3], galantamine[4]. Another medicinal drug, memantine[5], appearing in the year 2000, belongs to the class of antiglutamatergics which seek to reduce the neurotoxic effects of excessive glutamate release.

These drugs have usually been evaluated in therapeutic trials on the strength of four criteria: cognitive deterioration, functional level, global clinical impression and behavioral disorders. Most of the studies have a duration of 6 months, as recommended by health agencies, in order to identify a symptomatic effect.

For the cognitive criterion, the scale most commonly used is the ADAS-Cog (Alzheimer's Disease Assessment Scale-cognitive subscale) out of a total of 70 points. Patients spontaneously decline by an average of 4 points in 6 months, 6-8 points in 1 year, in non-linear fashion according to the stages of the disease. An average improvement of at least 2.5 points on this scale has been considered relevant in trials designed to reveal a symptomatic gain. After 6 months of treatment, the benefit of anti-acetylcholinesterase drugs is estimated at 2.7 points on average. According to the trials, patients also show less deterioration in their daily activities when receiving the treatment and not the placebo. The global clinical impression is also considered to be better. The number of patients that need to be treated in order to observe a stabilized or improved patient at 6 months varies between 5 and 8.

With memantine, the number of patients that need to be treated in order to observe a stabilization at 6 months is 6. Lastly, according to several studies, these medicinal drugs would seem to show a certain efficacy, albeit weak, on the associated behavioral problems (evaluated by the NPI) such as apathy, hallucinations, depressive symptoms, agitation and anxiety, particularly by preventing their onset. Although they are sometimes poorly tolerated (especially with regard to digestion), these medicinal drugs have not shown any serious adverse effects.

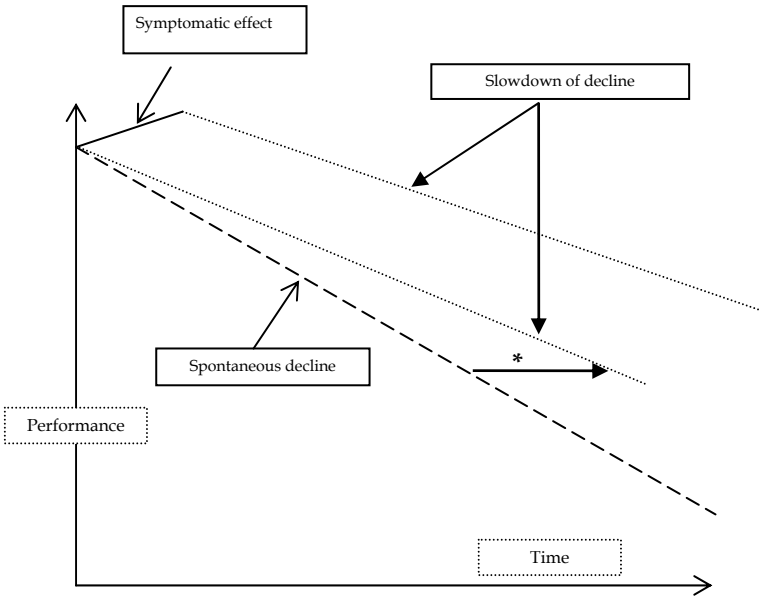
According to the recommendations of the EMEA (*European Medicines Agency*), a patient is considered as "responding" to the treatment if he improves by more than 3 points on the ADAS-Cog compared to baseline, without deterioration on a global appreciation scale, without functional deterioration and, if possible, without behavioral aggravation.

[2] Aricept®, market authorisation (MA) in 1997

[3] Exelon®, MA in 1998

[4] Reminyl®, MA 2001

[5] Ebixa®, MA 2002



Treatment objectives

* The horizontal arrow represents the time gain before reaching a given threshold of dementia

In France, antiacetylcholinesterasic drugs are indicated in mild to moderately severe forms of Alzheimer's disease (MMSE score of between 10 and 26 inclusive) and memantine for the moderate to severe stages (MMSE score of between 19 and 3 inclusive). In 2007, the *Haute Autorité de Santé* (French National Authority for Health)[6] recognized a major medical value for the 4 specialties. However, in the light of new clinical data and the experience acquired with these treatments since they were launched on the market, the authorities qualified the improvement of therapeutic value as "minor" in the context of global patient care. In the UK, the *National Institute of Clinical Excellence* (NICE) recommends further treatment if the MMSE score increases or does not fall 2 to 4 months after reaching the dose likely to have an effect.

According to an observation study conducted in France, the risk of entering an institution, after one year of follow-up, is lower in patients treated by antiacetylcholinesterasic drugs compared to patients who have never been treated.

In a randomized double-blind versus placebo trial, the patients initially receiving the placebo and then receiving the treatment after 6 months did not catch up with the patients who had received the treatment during those 6 months.

A double combination therapy associating a medicinal drug acting on the acetylcholine deficit and memantine has been studied for patients with a score of less than 19 on the MMSE scale. The association seems to be well tolerated. The potentiating effect of memantine has been tested positively with donepezil and rivastigmine.

The "Consensus on Alzheimer-type dementia at the severe stage" (French Geriatrics and Gerontology Society, 2005) recommends that discontinuation of the treatment should be based, both at institutional and outpatient level, on the evaluation of the benefit/risk ratio for each patient.

According to the parliamentary report of 2005[7], less than a third of patients with Alzheimer's disease in France are treated by these specific drugs. This number is increasing very slowly.

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[6] www.has-sante.fr

7. GALLEZ C. La prise en charge de la maladie d'Alzheimer et des maladies apparentées. Rapport de l'Office Parlementaire d'Évaluation des Politiques de Santé (Opeps), 2005: 256 p

The initial prescription and the annual renewal are carried out by neurologists, psychiatrists and general practitioners with expertise in gerontology. Patients are placed under special surveillance during treatment. This surveillance may be provided by the general practitioner. The daily cost of treatment is about 3 € for the antiacetylcholinesterasic drugs and 3.5 € for memantine.
These drugs have helped to lift the taboo surrounding the disease with patients and families and to change the image of the disease which no longer appears as a fatality for which there is no solution. They prompt doctors to invest more time in finding out about the disease and in treating the patients.

A non-pharmacological professional treatment of this disease seems to be essential

In view of the fact that Alzheimer's disease has an impact on not only the cognitive but also the psychological and social functioning of the patient, there is now a broad consensus insisting that patient care should not be limited to pharmacological treatment but should also include non-medicinal approaches. These therapies are widely applied in day centres, day hospitals, physiotherapy departments, memory centres and speech therapy practices, amounting to a not inconsiderable economic cost. There is in fact today a wide variety of non-medicinal therapies open to patients suffering from dementia. Some of these therapies adopt a psychosocial approach while others belong to the field of psychopathology. Others again have been developed on the strength of knowledge acquired from cognitive neuropsychology in the field of Alzheimer's disease, and yet others are based on physical or sensory stimulation. All of these techniques seek to optimize patient care by targeting, according to the therapy applied, different aspects of the disease such as cognitive abilities, dependence, mood and behavioral disorders or patient well-being. These techniques are extremely varied.

Principal non-medicinal approaches to Alzheimer's disease

Approaches	Techniques	Targeted aspects of the disease
Cognitive	Cognitive stimulation Cognitive re-education	Cognition, autonomy, satisfaction of the caregiver
Psychosocial	Reminiscence Validation Self-maintenance therapy Psychotherapy Therapy by simulated presence Art-therapy Animal-assisted therapy (dog)	Depression, behavior, quality of life, satisfaction of the caregiver
Environment adaptation	Re-education of orientation	Autonomy, cognition, social, quality of life
Sensory	Musicotherapy Luminotherapy Aromatherapy Snoezelen (multisensory stimulation) Gymnastics	Depression, behavior, quality of life, sleep
Motor	Motor training Gymnastics	Cognition, behavior, autonomy

Over the last twenty years, a very large number of articles have been published illustrating the benefits of these therapies on Alzheimer's disease. According to the studies, the reported improvement concerned different measurements. These benefits could be reflected in a reduction of the depressive symptomatology, a slower decline of certain cognition measurements, preserved autonomy in certain tasks of everyday life, attenuation of certain behavioral disorders, improvement in quality of life measurements or relative satisfaction reported by caregivers and/or the health care assistants responsible for the daily care of these patients. These results are encouraging inasmuch as they suggest that a global and multidisciplinary approach to the disease is likely to attenuate some symptoms and to contribute to a certain well-being for the patient.

Nevertheless, it is noteworthy that the vast majority of these results were derived from studies whose methodology leaves much to be desired, the main weaknesses of these studies being the absence of a control group, the absence of randomization, the absence of a procedure for evaluating in blind fashion and insufficient sample size. The scarcity of long-term measurements assessing the continuation of these benefits beyond the period of intervention is also most unfortunate. For some of these techniques, there are very few if any randomized studies. As for the benefits reported by meta-analyses including only those studies that meet the criteria of randomized controlled trials, these tend to be more modest in scope and in most cases, limited to the duration of the intervention.

One of the points contributing to the lack of credibility concerning the use of these therapies in the context of Alzheimer's disease is the failure to respect the uniform application of the same technique on the part of the health care assistants. For a given technique, the description of the treatment programs often varies from one study to another. The outcome is that, for most of these techniques, it is difficult to reach a consensus defining a program comprising clear indications on such essential points as the quality/training of the professionals likely to apply these techniques, the stage of severity of the patients liable to benefit from the said techniques, the duration of the program, the frequency of the sessions (daily, weekly, etc.), the details (group or individual service; with or without the participation of caregivers; relayed at home or not) or the very content of the sessions to be proposed.

Meta-analyses performed on the results of randomized trials evaluating the efficacy of non-medicinal treatment in dementia and/or Alzheimer's disease

Therapy/References	Number of trials*	Benefits reported
Cognitive training techniques Clare et coll., 2003	6	No improvement reported
Orientation re-education techniques Spector et coll., 2000	6	Improvement of certain cognitive and behavioral measurements which differed according to the studies
Therapy by reminiscence Woods et coll., 2005	4	Improvement of one measurement of autobiographical memory; of depressive symptomatology; of behavioral measurements; of caregiver's stress; of care assistants' satisfaction
Therapy by empathy Neal et coll., 2003	3	No conclusion due to insufficient data for conducting the meta-analysis
Musicotherapy Vink et coll., 2003	5	No conclusion due to insufficient data for conducting the meta-analysis
Luminotherapy Skjerve et coll., 2004	6	Improvement of certain measurements of sleep and circadian rhythm activity

Therapy/References	Number of trials*	Benefits reported
Aromatherapy Thorgrimsen et coll. 2003	1	Reduction of agitation and neuropsychiatric disorders
Multisensory stimulation Chung et coll., 2002	2	Improvement in measurements of apathy, mood and psychomotor capacities
Motor activity training Heyn et coll., 2004	30	Improvement of certain physical aptitudes and of certain cognitive and behavioral measurements which differed according to the studies

* Randomized or semi-randomized included

Lastly, since many of these studies were carried out on outpatients, it is difficult to know whether their results can be generalized to include patients living in institutions or whether the benefits expected for these patients are liable to be different. This is particularly regrettable in view of the very widespread use of these non-pharmacological therapies in institutions.

The role of informal caregivers remains insufficiently recognized

The informal caregiver is defined as a member of the dependent person's family circle who has not been trained for this task, and who provides care on an unpaid basis. To properly understand the aid given, it is necessary to view the caregiver as someone who shares a history with the assisted person going back to before the implementation of the caregiving relationship, but also as someone who interacts with all the informal caregivers (co-caregivers) and professional carers. Historically, the family has always been the veritable backbone of the home care dispensed to dependent elderly people, in particular subjects suffering from Alzheimer's disease. Long regarded as "in the nature of things", this aid has not aroused particular interest on the part of the public authorities. With the development of home support policies and the establishment of specific professional support, the evaluation of the needs of these people has led to an awareness of the importance of this informal care.

This recognition dates back to the introduction of the "specific dependence benefit" and then the "personal autonomy allowance," making it possible to pay an unqualified person for the assistance he or she provides to an elderly dependent. Alzheimer's disease has on its own greatly contributed to reinforcing visibility in this area: one of the proposals of the Girard Report (September 2000) was to implement a special allowance for informal caregivers. The "Old Age Solidarity Plan", presented in June 2006, stressed the need to provide support for family caregivers, in particular by establishing their right to respite or relief. This respite will be based on recourse to temporary accommodation or the use of new modes of support such as the "Baluchon Alzheimer" developed in Canada. Finally, the Family Conference ("Conference de la famille") in 2006, devoted to "inter-generational solidarity within and on behalf of families", aimed at providing greater recognition and support for family caregivers and promoting their role.

In France, it is still difficult to estimate the number of caregivers for people suffering from Alzheimer's disease. The HID survey (Handicap-Disability-Dependence)[8] puts the number of caregivers for persons aged 60 years and over at 3,700,000, without specifying the proportion of persons with Alzheimer's disease. The caregivers are spouses in half of the

[8] The results were obtained from a sample of 8,800 persons aged 60 years and over and living at home in 1999.

cases and children (or their spouses) in about one third of cases. Caregivers are on average aged 62 years, and in 66% of cases, are women. In fact, there are two distinct populations of caregivers represented by elderly spouses and children. Among persons aged 60 years and over in need of assistance, half of them would appear to be assisted only by their family circle, 29% receive aid combining informal and professional help and 21% are assisted only by health care professionals.

With regard to the caregivers of persons suffering from Alzheimer's disease, and referring to the REAL.FR9 cohort, the data concerning caregivers are reasonably comparable with those for the HID survey mentioned above: in more than half of the cases the caregivers are spouses (they are children in more than a third of cases). The caregivers are mostly women (59%) and their average age is 64.7 years.

At home, the number of hours of assistance given by the caregiver is considerable – two to three times greater than the amount of professional help. The volume of informal aid declared by the caregiver varies considerably, depending on his or her lifestyle (notion of cohabitation with the assisted person) and the characteristics of the person receiving help (level of severity of dementia). The family continues to play an important role, even after the patient has been admitted to an institution, both in terms of maintaining contact with the old person and of assistance, which continues in 30 to 50% of cases.

The impact on the caregiver's own life of the assistance given has received considerable attention in the literature which brings out the limits of such assistance. There are frequent repercussions on the caregiver's mental health, with high risks of depression (30%), anxiety and sleep disorders (in 80% of cases). Moreover, repercussions on the caregiver's physical health are by no means negligible and would seem to be linked to stress or to less frequent recourse to health care on the part of the caregivers themselves.

The caregiver's vulnerability may also be assessed by measuring how he or she experiences this care. Thus, the concept of "burden", and the tools for measuring it as developed by Zarit and others, studies the impact of the aid on the caregiver's own life from different angles (physical, psychological, socio-economic and financial). It is important to be on the look-out for a "heavy" burden because it is a major determinant of a breakdown of home help resulting in placement in an institution. Many factors may contribute to the level of burden experienced by caregivers, some of them having to do with the characteristics of the caregiver (sex, kinship), others having to do with the person receiving help (severity of dependence, nature of the disorders), and yet others are associated with the helping relationship.

The caregiver can also experience the assistance given in a positive way (gratification, recognition) and this will serve to offset the level of his or her burden. This may partially explain why certain caregivers are reluctant to have recourse to professional caregiving and continue to cope on their own, sometimes to the point of exhaustion, hence the need to detect such cases in advance.

A periodical evaluation of the aid given to persons suffering from Alzheimer's disease should therefore be carried out in order to identify the problems encountered by caregivers and to propose appropriate measures. In the course of his/her "career", a caregiver will live through certain key moments such as the pronouncement of the diagnosis, the recourse to professional care, the breakdown of home care and the death of the person receiving aid.

[9] The results were obtained from a sample of 686 persons suffering from Alzheimer's disease, living at home, having an identified informal caregiver and followed up in a French university hospital between 2000 and 2002.

The question of help for caregivers is often raised. Indeed, caregivers have access to available and known resources (relief services, support groups, patients' associations), but the evaluation of these kinds of operations are seldom based on true research work. The few studies published in this field have, in certain cases, shown a beneficial effect of support programs with regard to entering an institution or the ability to manage behavioral disorders. Such measures must of course be compatible with the patients' quality of life.

Meanwhile, research on informal caregiving has grown considerably: there were 1,954 publications recorded in the *Medline* bibliographical base for the period 2001-2006[10] compared to none at all before 1985. As a first step, the various concepts of aid were discussed: the personality of the caregiver with his/her ability to cope, the impact of aid on the caregiver's life together with the study of the burden felt, and the study of these determining factors. More recently, various attempts have been made to reduce the consequences of the help given on the caregiver's own life. All in all, this informal caregiving is important because it postpones the time when the patient will have to enter an institution. And it is all the more essential to quantify this informal caregiving since it is likely to diminish in the future, as a result of demographic trends and increased life expectancy, and will have to be replaced by professional caregiving. This "shortfall" of caregivers looks set to grow due the social and cultural changes already underway and visible (reconstituted families, women less available than before, children living further away). Changes in social values (desire for individual autonomy, emphasis on the generational family, the role expected of the State in providing support for its most vulnerable citizens) will need to be depicted and analysed.

The high frequency of Alzheimer's disease makes it a major public health issue

In 2007, the number of people aged 60 or over stood at 13.1 million, i.e. 21% of the French population (source National Institute for Statistics and Economic Studies – INSEE). If current trends in life expectancy continue at the same rate, by the year 2050 the number of people aged 60 years and above will account for 35% of the population (22.4 million).

A study which does not include an active search of cases of dementia, in particular Alzheimer's disease, means that probably only cases diagnosed and treated by the health care system are taken into account, and the severe rather than the moderate forms at that. The number of patients living in institutions is underestimated, in particularly the very old (>85 years). This is for the most part due to diagnostic difficulties and to society's greater tolerance of cognitive loss among the older members of the population. Part of the variation shown in the figures reported from one study to another may be explained by the greater or lesser proportion of dementia detected. Subjects are not followed up for numerous reasons, some of which are directly linked to the development of the dementia pathology, as for example the admission to an institution. Biostatistical modelling should make it possible to take some of these phenomena more into account.

Studies covering the population before the age of 65 years are few and far between. Before this age, the prevalence is estimated at between 0.05 and 0.1%, i.e. about 32,000 patients in France. Based on analyses of European data provided by the Eurodem group, the prevalence

[10] The search included all articles referenced with the keyword caregivers (MESH) – but selecting only those in which they represented the principal subject of the article – in the population aged 65 years and over.

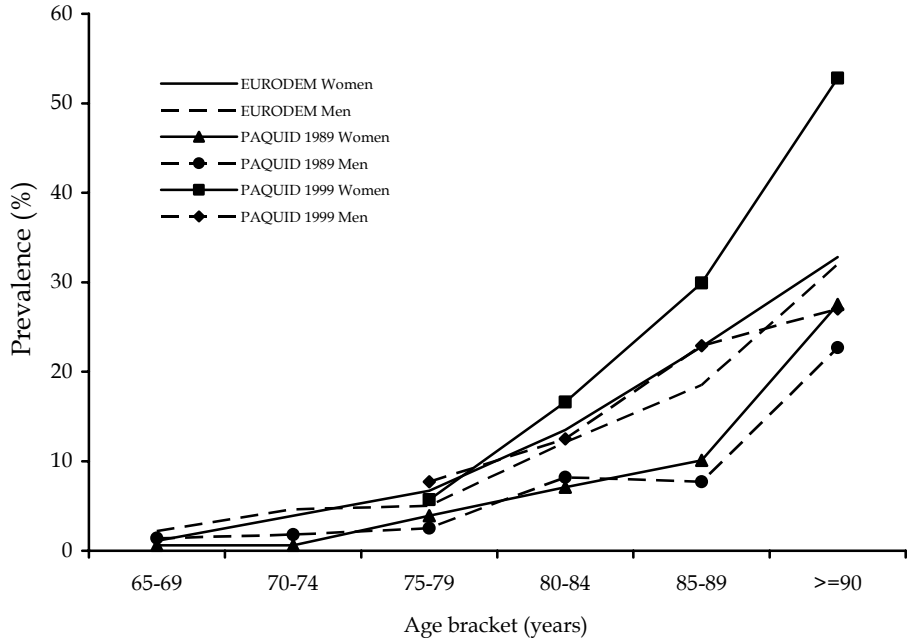
rate of dementia in subjects aged over 65 years is estimated at 6.4%. The prevalence increases with age.

How is it possible to give estimations on the number of cases of dementia and Alzheimer's disease in France in 2007, in the absence of any reliable health indicators or any registers providing an exhaustive and long-term record of cases? If no such data exist today, it is also because the diagnosis of dementia is in many cases not made, even at the severe stages of the disease. After 65 years, the main source of data on the prevalence of dementia in France comes from the PAQUID survey (a cohort study of old persons in the Aquitaine region of France since 1989). The prevalence was estimated in 1989 and then re-evaluated in 1999 on the survivors of the original cohort aged 75 years and above. In the PAQUID study, the prevalence in 1989 among the persons aged over 75 years was 8%. Largely as a result of a more precise diagnosis and increased life expectancy, this figure was revised upwards after 10 years of follow-up, with a rate of 18%. We do not have more recent data at our disposal and there is no study currently in progress capable of providing updated information on the descriptive epidemiology of dementia.

It is not possible to say whether the incidence of this disease has really increased in recent years. Changes in classifications (DSM III then III-R and IV, ICD-9 and then 10) over the last 20 years, and new survey methodologies, not to mention an increased awareness of the diagnosis of dementia, all combine to make comparisons difficult. It is possible that the apparent increase reflects a genuine trend, linked either to an increase in the duration of the disease (itself linked to an increase in life expectancy or better patient care) or to a genuine increase in incidence.

In terms of incidence, the analyses made from eight European studies show an average rate increasing sharply from 2 per 1000 persons per year between 65 and 69 years to 70 per 1000 persons per year after 90 years. No study of very old subjects has been carried out in France. The results of a recent meta-analysis on European and American data indicate that the prevalence figures lie within a fairly wide range between 15 and 40%, with the incidence of figures ranging from 60 to 100 per 1000 persons per year.

Extrapolating these data to the year 2004 census, it would appear that there are more than 850,000 cases of dementia in France. Globally, Alzheimer's disease represents about 70% of these cases, the others being vascular (10%) or mixed (20%), with virtually three times as many women as men affected, and with 230,000 cases concerning the very old (over 90 years). There are 300,000 cases of severe dementia. At world level, an international analysis based on a consensus methodology between experts (*Delphi consensus*) estimates the number of cases of dementia at 24.3 million, with almost 4.6 million new cases each year. The number of cases is expected to double every 20 years, thus concerning over 80 million persons in 2040.



Prevalence of dementia in men and women

Eurodem meta-analysis data on studies conducted in the 1990s (Lobo et coll., 2000); Initial data of the PAQUID study (1988-1989) (Letenneur et coll., 1993); Data at the 10-year follow-up of the PAQUID study (1998-1999) (Ramaroson et coll., 2003)

The identification of risk factors and protective factors opens up prospects for prevention

Ever since the first studies were published in the years between 1980 and 1990, the list of potential risk factors for Alzheimer's disease has grown much longer. Although we can now call upon the results of cohort studies and a few randomised trials, it remains difficult to isolate the factors for which an intervention study should be proposed. The results of the observation studies with menopause hormone replacement therapy or non-steroid anti-inflammatory drugs conflict with those of randomised trials in women aged over 65 years (negative trial, trial discontinued due to serious adverse events).

Nevertheless, the search for potentially modifiable risk factors is one of the major public health challenges posed by Alzheimer's disease. Although this is a condition that occurs most often at an advanced age, increasing attention is now being paid to the subject's entire life, particularly the period between 40 and 50 years, rather than his or her characteristics in the years leading up to the diagnosis. The factors leading to chronic diseases at advanced ages may originate in the very early years of a person's life or accumulate throughout life. Certain factors such as high blood pressure may also have different effects at different periods of life.

As far as socio-demographic criteria are concerned, age remains the principal risk factor of Alzheimer's disease, its incidence doubling by periods of 5 years after the age of 65. But other factors have also been identified:

- Female sex: the incidence of the disease increases in women after 80 years. Many hypotheses have been advanced in explanation of this fact although a selective survival bias cannot be ruled out;
- A weak academic level (small number of years of formal education or low level attained) is very frequently associated with an increased risk of developing Alzheimer's disease in the cohort studies. The French data show a greater risk for subjects who have not passed the school-leaving certificate. These findings tally with the hypothesis according to which subjects with a high educational level possess a greater cognitive reserve capacity which in turn enables them to express their disease in a different way and to delay its clinical expression.

With regard to lifestyle, a strong social network and leisure activities are cited as potentially protective factors. Activities such as reading, games, dancing, gardening, travel and DIY have been linked to a reduced risk of developing Alzheimer's disease. However, it is difficult to discard the hypothesis of a halt to these activities in the pre-symptomatic stages of the disease, which would be expressed by an exaggeration of the effects of these factors. Recent longitudinal data have shown an increased risk among smokers, whereas smoking has long been suggested to have a protective influence. The moderate consumption of wine or other alcoholic beverages would appear to be associated with a lower risk of Alzheimer's disease. Biological mechanisms have been advanced in this sense, but the effect may be related to a particular lifestyle. Large observational studies involving several thousand subjects followed up over periods varying from 2 to 15 years have demonstrated a protective effect of intense and/or sustained physical activity over time, both with regard to the decline of cognitive functions and the occurrence of dementia.

There is a proven association between cardiovascular risk factors and vascular-type dementia – more frequent in cases of high blood pressure – but the connection between vascular factors and Alzheimer's disease is less clear. The observed effects differ depending on the period of life considered. Thus, all the studies report an association between high blood pressure measured 20 to 30 years previously and cognitive decline or the onset of dementia, with a higher risk when the high blood pressure is not treated. A randomized study seeking to lower systolic blood pressure has shown a decreased risk of Alzheimer's disease, but this has not been confirmed in other trials. In contrast, studies show that a low level of blood pressure is more often associated with dementia after 80 years.

High levels of cholesterol are associated with an increased risk of Alzheimer's disease, especially when they are recorded between 40 and 50 years. Early studies of prevention fail to show the beneficial role of treatment with statins. Diabetes is usually associated with a lower level of cognitive performance, a more pronounced decline of cognitive functions over time but also with the onset of Alzheimer's disease. However, the definition of diabetes varies from one cohort to another; the same holds true for the effect on the risk of dementia, particularly in light of the age of the diabetes or the existence of a specific treatment.

It is essential to take all vascular risk factors into account simultaneously in quantifying their respective roles, but also in attempting to develop risk factor scores, as in cardiovascular diseases.

With regard to medical history, depressive symptoms are associated with an increased risk of Alzheimer's disease, although it is difficult to ascertain whether they represent a genuine risk factor or a prodrome of the disease. Several teams have mentioned the role played by a history of heart problems (atrial fibrillation, heart or coronary failure) in the impairment of cognitive functions, but not all their findings concord. The role of anemia remains a matter for debate because of the scarcity of longitudinal studies.

The aging process, like the decline of the cognitive functions, may be responsible for changes in dietary habits and may lead to nutritional deficiencies. The relationship between weight and the risk of Alzheimer's disease has long been established. Early work showed that a particularly low body mass index was associated with the risk of dementia and Alzheimer's disease, but recent studies have emphasized the positive relationship between obesity and the risk of dementia or a decline in cognitive functions.

The association between a deficiency in vitamin B12, vitamin B6 or folate (vitamin B9) and the risk of Alzheimer's disease remains unclear. There is an inverse relationship between plasma homocysteine levels and the status in vitamins B6, B12 and folate (food intake, plasma levels). Hyperhomocysteinemia would appear to be a cerebral vascular, coronary and peripheral risk factor. Several cohort studies have found a relationship between antioxidant intake and a reduced risk of dementia or cognitive decline, but with certain discrepancies. The results nevertheless point to a possible role of vitamin E rather than vitamin C , and also carotenoids and selenium. The results of randomised trials in elderly patients (healthy subjects, patients suffering from Alzheimer's disease or MCI) are not yet sufficiently convincing to justify specific recommendations for the prevention of dementia. The protective effect derived from the consumption of fish rich in omega-3 polyunsaturated fatty acids on the risk of dementia has been described in various longitudinal studies concerning elderly subjects.

The epidemiological analysis of the relationship between consumption of nutrients and cognitive decline is complex and it is highly unlikely that any one compound plays a major role. The notion of a more holistic approach to nutrition should be developed. The interest shown in the Mediterranean diet is a case in point: convergent studies show a reduced risk of cardiovascular disease, mortality and possibly Alzheimer's disease with a diet characterised by high intakes of vegetables, fruit and cereals, unsaturated fat, moderately high intakes of dairy products and wine and low intake of meat.

Finally, other factors (head injuries, aluminum in drinking water, anesthesia, etc.) have been discussed but their association with Alzheimer's disease is based on disputed data.

It is important to stress the dearth of epidemiological studies that take into account all the suspected risk factors. The search for risk factor scores should be continued, as has been the case in the cardiovascular field. Efforts must focus on modifiable risk factors with the aim of developing preventive strategies for Alzheimer's disease. The study of risk factors related to lifestyle should be based on a global approach to these factors, and will therefore require the presence of multidisciplinary teams: for example, the study of nutritional factors should include a record of food intake and an analysis of dietary habits.

The time for action can no longer be put off. In the majority of the listed trials, the primary objective was not cognitive evaluation. With regard to those factors for which an array of arguments already exists, there is a need to launch new projects. In particular, the effects of medicinal therapies (antihypertensive treatments, care of diabetes and hypercholesterolemia) must be evaluated, along with the effects of nutritional factors (via changes of dietary habits) or programs encouraging physical exercise, intellectual or cognitive activities and the social network.

Access to diagnosis remains a problem in France

Alzheimer's disease is not considered a priority in general medical practice and is even ignored in many cases. A survey on the implementation of the recommendations of the ANAES was conducted by medical officers from the national health insurance system in 9

French regions on 3,510 patients in 2000-2001. The survey shows that the diagnostic procedures of Alzheimer's disease are on the whole in line with official recommendations: recourse to a specialist in nearly 95% of cases for treated patients (only 30% of patients), with a score measured on the MMSE – the universally recognized psychometric test for measuring the severity of dementia – in 85.5% of cases, and brain imaging performed in 85% of cases. On the other hand, dysfunctions appear when the patients do not have recourse to the health care system or when complaints are lodged against doctors who do not program a diagnostic examination. Thus, in the "3 Cités" study conducted in three French cities (Bordeaux, Dijon and Montpellier), consultation of a general practitioner and in particular recourse to a specialist varies considerably depending on the subject's age.

Proportions of consultations with a general practitioner for cognitive disorders and of recourse to a specialist in subjects presenting with prevalent dementia ("3 Cités" study, 2002, N = 201)

Age (years)	Consultations with a general practitioner (%)	Recourse to a specialist (%)
65-74	65.8	55.0
75-79	64.7	42.3
80 and above	55.1	19.7

The results show that 4 out of 5 patients aged at least 80 years did not have access to the recommended diagnostic procedures. The European *Facing Dementia Survey*, carried out in 2005 in 6 countries (France, Great Britain, Germany, Italy, Spain and Poland), shows that, according to the doctors, only 4 out of 10 patients consult for the first time at a mild stage of dementia, 54% at a moderate stage, and 7% consulting only at a severe stage. The French results are within the average for Europe as a whole. The average lapse of time between the onset of the disorders and the diagnosis is 24 months in France. This is the second worst score recorded in Europe after Great Britain (32 months), the shortest time being observed in Germany (10 months). In other words, Alzheimer's disease and the other types of dementia are often neglected in the general population, especially after 80 years.

There are many causes of this subdiagnosis of dementia in the population. They can, to a large extent, be superimposed on the causes of the dysfunctions in patient care. Four categories may be distinguished:

- Causes linked to special difficulties in recognising the disease due to its semiologic characteristics
- Causes linked to the image of the disease in the population
- Causes linked to doctors' attitude towards the disease
- Causes linked to the lack of relationship and coordination between the social and health spheres

Little is known about the precise consequences of the subdiagnosis of dementia and very little work has been devoted to the value of routine screening, including cases where the patient denies the situation. This explains why the national recommendations for early detection of dementia, and more specifically Alzheimer's disease in France, as in the United States and Canada, have been mainly based on a consensus of expert opinion.

If we accept that the available treatments (pharmacological and non-pharmacological), as well as the information and support given to the caregiver, have an effect on the progression of the disease, then any delay or fault in diagnosis can be seen as an opportunity lost for the patient. In addition, unawareness of diagnosis exposes the patient to the risks related to

difficulties in everyday activities, for example driving. Another consequence concerns inappropriate recourse to the health care system, and in particular to emergency hospitalization. Lastly, the lack of diagnosis – and thus of care – leaves the family feeling distraught and at a loss, without help, without means of preventing crisis situations and without the possibility of anticipating problems related to dependence.

In the future, therapeutic interventions will have to take place as early as possible: the development of new medicinal drugs designed to slow down and counter the pathological process will make it necessary to identify patients suffering from Alzheimer's disease at the early, pre-dementia stage.

Health care has developed considerably in recent years but still needs to be evaluated in relation to needs

Data on the provision of care in France come mainly from the authorities responsible for the management of the elderly (Dhos, DGAS, Drass), institutes and services producing statistical data (Drees, Irdes, Insee, FNORS) and federations (Fédération Médéric Alzheimer, Fédération nationale des CMRR). An assessment was drawn up on the occasion of the Opeps report (Parliamentary Office for the Evaluation of Health Policies) in 2005[11] and updated for the purposes of this expertise. However, this analysis does not set out to compare needs with the existing structures in France.

Health care for Alzheimer's disease falls into three categories: diagnosis, information/coordination, and medical and socio-medical care. Most of these services have greatly increased their capacity and facilities over the past three years.

A review for the year 2007, covering the mechanisms for supporting and accompanying patients and their caregivers, has just been published by the Fondation Médéric Alzheimer[12].

Types of services and structures for the care of persons suffering from Alzheimer's disease in 2007

Type of services	Structures	Number of structures in metropolitan France (rate per 1000 persons aged over 75 years
Diagnosis	Memory consultations	3661
	Resources and Research Memory Centres (CMRR and hospital centres)	251
	Neurologists in private practice	763[2] (0.97)
Information/coordination	Local information and coordination centres (CLIC) labelled according to the scope of their mission	5383
	Gerontological coordination networks	521
	Support structures for caregivers	237 (0.06)[2]

[11] GALLEZ C. La prise en charge de la maladie d'Alzheimer et des maladies apparentées. Rapport de l'Office Parlementaire d'Évaluation des Politiques de Santé (Opeps), 2005: 256 p (The care of Alzheimer's disease and related diseases)

[12] Annuaire national 2007. Dispositifs de prise en charge des personnes atteintes de la maladie d'Alzheimer ou de maladies apparentées et dispositifs d'aide à leurs aidants familiaux. (National directory 2007. Mechanisms for providing care to persons suffering from Alzheimer's disease or related diseases and mechanisms for helping their family caregivers). Fondation Médéric Alzheimer, Paris, 2007: 446 p. Website of the Fondation Médéric Alzheimer: www.fondation-mederic-alzheimer.org/

Type of services	Structures	Number of structures in metropolitan France (rate per 1000 persons aged over 75 years
Medical and socio-medical care	Doctors in private practice (general practitioners, psychiatrists, neuropsychiatrists)	114,227 (11.83)[2]
	Home nursing care services	80,643 places (18.25)[2]
	Day reception centres	4,085 places[1]
	Temporary accommodation	2,500 places[1]
	Accommodation establishments for the old	
	EHPA (hospital establishment for old persons)	666,997 places[2]
	EHPAD (hospital establishment for dependent old persons)	671,000 places[2]
	Home-help services	
	Hospitals	

[1] Source: DGS, Review of the implementation of the Alzheimer Plan for health systems at 31 December 2006
[2] Source: Opeps, Gallez Report on Alzheimer's disease and related diseases, 2005
[3] Source: Ministry of Health and Solidarity, 2006, http://www.personnes-agees.gouv/fr

Different countries (the United States, Germany, Great Britain) have experimented with procedures for coordinated care based on models of support prioritised according to the needs of patients (Appendix 3). This type of innovative approach involves successively a *disease/care manager* and then a *case manager*.

As part of initiatives for health promotion, the disease/care programs, initially developed to meet the needs of persons suffering from chronic diseases (diabetes, heart failure, asthma, etc.), are principally designed to encourage therapeutic education by prompting the patients themselves to take more responsibility for their condition. The programs seek to increase the knowledge of the patients, and possibly of their family, and to develop their skills. They also tend to promote coordination of care (assistance in the guidance of patients, planning consultations and care, etc.). Specifically, the most common form of intervention is through telephone calls made by a health care professional. Over and above the technical aspect of the interviews, the ability to develop empathy with the patient is considered of paramount importance.

When the need for care becomes more acute and the risks to the patient reach a given threshold, an additional level of action consists in introducing a more personalised type of care through the presence of a case manager. Case management involves developing a support function for the individual treatment of the most difficult situations. This support is not limited to health matters; it also embraces the social dimension. Thus, the case manager – most often a nurse - is a unique and special correspondent, in charge of the patient's global care. The case manager is also a direct contact between the person, his/her family and the family doctor. As a matter of principle, the manager's action is continuous (including in situations of hospitalization). This type of action has been applied to the follow-up of the elderly in different countries and has proved successful in improving the accessibility to help, the use of care, autonomy and compliance with the rules of good practice, while at the same time reducing the recourse to institutionalization and hospitalization and cutting down on medical costs. In France, the use of case managers to coordinate care for people with Alzheimer's disease has also been experimented, particularly in certain regions, and its evaluation is currently underway.

Image of the disease in the society has acted as a barrier to its treatment

Health sociology, which has attracted few researchers compared to other areas of health, has tended to concentrate more on pathologies whose gravity has long been recognized, e.g. cancer, or which have raised societal issues (AIDS). But it is also likely that the assimilation of Alzheimer's disease with old age has to some extent blinded sociologists to the interest of this condition.

This poor sociological output has given rise to a body of mediocre results: investigations are to a very large extent qualitative (and thus based on small samples) and should really be repeated for validation purposes, but this is rarely the case. An analysis of the various publications suggests that sociologists are more responsive to questions pertaining to the science of sociology itself rather than to societal demand: the theme of Alzheimer's disease lends itself to theoretical research on individual identity (the question of "self-maintenance") or on social identities (the diversity of representations of the disease), but it can hardly be said to be motivated by the questions posed by society.

We may nevertheless note three areas of investigation which have yielded significant results, although the surveys in question would need to be completed or validated outside the context of the USA.

One of the main areas of sociological investigation as far as Alzheimer's disease is concerned is the experience of the disease, in particular the question of maintaining individual identity in spite of the development of the disease. From the sociologist's point of view, social identity is constructed by virtue of interaction with others. By studying the changes in interaction with the patient's circle of family and close friends (family, professional or, more broadly, societal circle), researchers have identified strategies for the "maintenance of self" vis-à-vis other people. These strategies show to what extent patients generally remain active faced with their condition, and how members of their circle of family and close friends can use these strategies as a means of maintaining personal identity. The analysis of the experience of the disease reveals that the disorders linked to it must be appreciated in the light of the reactions of the patient's circle of family and close friends.

The second area of research investigated by sociologists and related to Alzheimer's disease is that of the social representations of the disease. The major conclusion that we can draw from reading these investigations is the diversity of the representations: firstly, according to social or cultural groups, and secondly, according to the position of the actors in relation to the disease. A certain body of research focuses on differences depending on the cultural context, since certain cultures attach different meaning and weight to the loss of memory or cognitive abilities. In addition, the disease assumes a different sense depending on whether one is the patient, a member of the close family circle or someone not directly concerned by the disease. Thus, the media tend to dwell on the "fear and anguish" aspect, whereas those most closely affected by the disease (patients or caregivers) see these negative images in perspective. These "non-specialist" representations may also conflict with scientific representations when the diagnosis is pronounced.

Some research work has concentrated on associations concerned with Alzheimer's disease, either with a view to analysing their origins and development from the social angle or to examining their role. From these analyses, associations emerge as acting more as pressure groups seeking to place the disease in the forefront of the socio-political scene rather than playing the role of spokesmen for the patients.

One of the most striking results emanating from the analysis of the sociological production with respect to Alzheimer's disease and related dementia is ultimately the contrast between, on the one hand, the actual experience of the disease (where studies have shown that

patients and their family circles possess skills for coping with their situation, albeit not without pain or suffering), and on the other hand, societal representations characterised by negative images of fear which are sometimes excessive and pernicious.

The socio-medical cost of the disease is far higher than its medical cost

Economic studies of Alzheimer's disease mostly consist of studies of the cost of the disease and the cost per patient, together with medico-economic evaluations of the drug therapies. On the other hand, there are very few studies concerning the evaluation of non-pharmacological health care. Moreover, there is a lack of research that could give the public authorities a broad and macro-economic perspective on such subjects as the arbitration between home care and residential care, the question of comorbidities, the predictors of hospitalization, and the economic interest of early diagnosis. It is not that these issues are not addressed, but rather that they are considered in the context of small studies posing problems of representativeness.

On the strength of 71 English-language studies of costs published between 1985 and 2000 (of which 21 corresponded to scientific criteria), the overall assessments of the cost per patient ranged from 1,500 € to 91,000 € for the year 2000. The differences are explained by the methodologies adopted and the care systems considered. The cost perimeter varies in function of the research objectives. In the perspective of direct payment by insurance for medical care, the focus will be on the medical costs. In the perspective of the social welfare system, the direct social and medical costs financed by the public authorities will be submitted to analysis – possibly extended to informal direct costs in order to reflect the presence of family solidarity alongside public solidarity. Finally, from the societal point of view, the costs will be considered in the widest context.

There is general agreement that Alzheimer's disease is an aggravating factor in the cost of elderly patients, the global multiplying factor varying between 1.5 and 2. The social-medical cost is greater than the medical cost, and the family is the principal contributor. The cost rises in line with psychic deterioration, due to the institutionalization of the patients, regardless of the scale used to measure this deterioration. It increases when the patient's ability to perform everyday activities diminishes. The increased costs, both direct and indirect, are reinforced by behavioral disorders and comorbidity. The informal caregivers for patients suffering from Alzheimer's disease at a severe stage devote more of their time to care, are more often absent from work and make a greater financial contribution.

Drug therapies in Alzheimer's disease has given rise to numerous cost/effectiveness studies, punctuated by the advent of new medicinal drugs and virtually all financed by the pharmaceutical industry. A large number of pharmaco-economic studies concern acetylcholinesterase inhibitors (donepezil, rivastigmine, galantamine), used primarily for the mild to moderate stages of the disease, or antiglutamatergics (memantine) used for the moderate to severe stages.

Depending on the case, the result indicator may be the stabilization of the MMSE level, reduced recourse to hospitalization or delayed recourse to institutionalization and its effect on the amount of informal care. Some studies use a synthetic indicator such as *Qaly* (quality of life per year of life gained). But it is still a delicate matter to assess the quality of life of patients whose verbal communication has often deteriorated. The *National Institute of Clinical Excellence* (NICE, 2005) in the United Kingdom has used this type of indicator for the medico-economic evaluation of medicinal drug treatments in Alzheimer's disease.

In fact, the different studies do not completely converge and are even sometimes contradictory. It is therefore difficult, from a comparison of these studies, to draw definitive conclusions based on consensus on the cost/effectiveness character of the medicinal drugs.

In France, several estimations have been made of the cost of Alzheimer's disease. For example, in 1993, the average net annual cost of Alzheimer's disease was calculated to be 18,265 €. The Organisation for Economic Cooperation and Development (OECD) put forward the figure of 19,581 € for the total cost per patient in 2000. The Opeps[13] report puts the average annual cost per patient at 22,099 €, including 5,791 € in medical expenses and 16,307 € in socio-medical expenses (of which 55% is borne by the families). It is the socio-medical, and not the medical component that accounts for the bulk of spending by the public authorities on Alzheimer's disease (90%). The proportion of medical expenditure is currently very limited: an average of 369 € per patient and per year. Lastly, the disease is absolutely ruinous for the patient (12,146 € on average per family and per year in 2004), whereas the average retirement pension in that year was 14,400 €: 10,800 € for women and 18,600 € for men.

These studies bring home very clearly the economic problem posed by the health care required for all patients suffering from Alzheimer's disease. They give decision-makers an indication, more or less precise, of the size of this problem.

Simple scenarios can be built up from the estimation of an overall cost of the disease. The scenario envisaged by Opeps is of the "all other things being equal" variety. Gross domestic product (GDP) and the price of socio-medical services is growing at a rate of 1.5 points and salaries at the rate of 1.6 points. The Opeps report indicates that total expenditure will grow from 9.9 € billion in 2004 to 15.2 € billion in 2020 and to 28.9 € billion in 2040 (1.04% of GDP). A second scenario consists in introducing a qualification of socio-medical services and aligns the growth of their remuneration on that of salaries. Total expenditure in this case comes to 19.3 € billion in 2020 and 50.4 € million in 2040 (1.82% of GDP).

All in all, our economic knowledge of the consequences of Alzheimer's disease in France remains inadequate and the available economic studies are of uneven quality – some of them focus only on very small numbers of patients over periods of times running from 3 months to 1 year. There is no individual or longitudinal follow-up of the consumption of resources, at home or in an institution, for this kind of patient and the long-term economic effects are not incorporated in the calculations. The cost estimations chiefly concern the medium and severe stages of Alzheimer's disease and there is little data on the first phase of the disease, nor indeed on the costs for the very severe or terminal phase.

One of the compelling hypotheses emerging from the cost-effectiveness analyses is to the effect that the cost of care is related to cognitive ability (as rated by the MMSE), which is supposed to determine the question of institutionalization. But it is difficult to establish a clear correlation between institutionalization and the cognitive disorders assessed by the MMSE. Institutionalization also depends on the patient's ability to perform the essential activities of daily life, the emergence of behavioral disorders, the economic, social and family situation of the caregiver and his/her ability to cope.

A pre-condition for ensuring the quality of economic studies is a precise delimitation of the target population, of the scope of the care in question and of the cost of producing the various services. This condition is not currently met because of the large number of undiagnosed cases, the diversity of clinical practices and the variability of the costs.

[13] GALLEZ C. La prise en charge de la maladie d'Alzheimer et des maladies apparentées. Rapport de l'Office Parlementaire d'Évaluation des Politiques de Santé (Opeps), 2005: 256 p

Furthermore, most patients suffer from more than one pathology, and it is unclear what proportion of the costs is strictly attributable to Alzheimer's disease: most of these patients are treated "globally" in the context of systems which make no distinction between physical and psychic dependence.

However, the major difficulty stems from the fact that the costs as well as the benefits of the care of patients suffering from Alzheimer's disease are chiefly bound up with the socio-medical and domestic spheres. In other words, the conclusions reached by the economic studies are heavily influenced by the methods used for evaluating informal caregiving. The amount of time devoted to care is often measured over a short period and then extrapolated to a long period, due to the lack of long-term cohorts. The time given to care can change from one day to the next and the intensity of this care may also vary. It is difficult to assess the amount of care, since such care falls within the family and domestic province. Moreover, the value of informal care can be estimated using different methods: by the caregiver himself/herself, by the allowance paid to caregivers by the government, by the cost of replacing the caregiver by a professional , or by the cost of the appropriateness for the caregiver of devoting his/her time to the parent suffering from dementia. Particular mention should be made of the body of work dealing with the different relief formulas proposed to caregivers (in particular day care centres) and the possibility of balancing the budget of these centres through the resulting cost savings. Various studies have looked at the financial performance of the relief services. There is a positive benefit for the caregiver when using a day centre on both a short-term (3 months) and long-term (1 year) basis. The costs are lower over the longer period, which suggests that caregivers should be encouraged to get involved in such programs at an early stage. Less recourse, on the part of the caregiver, to acute hospitalization (but not to emergencies) was also reported when a "case manager" was present.

Recent public policies and government plans reflect a growing awareness of the size of the problem

Alzheimer's disease and related syndromes were to all intents and purposes ignored by policymakers until the end of the twentieth century. One of the most striking illustrations of this neglect was the report published by the Haut Comité de la Santé Publique (High Level Public Health Committee) in 1998. The report was supposed to review the major public health issues in France at that time but made no mention of either Alzheimer's disease or dementia, despite the fact that these diseases were already affecting at least 500,000 French people.

It was only in the early years of this century that the political forces and health authorities came to terms with the size of the problem. This was because of the more pronounced aging of the population (particularly after the relative pause brought about by the fall in the birth rate after the First World War), the emergence of methods and treatments of these diseases, the media attention given to certain famous cases such as Ronald Reagan, and the actions of the various associations representing the families of patients and grouped together in a single national association, the Association France Alzheimer.

Given the increase in the number of persons suffering from Alzheimer's disease throughout Europe, all the countries are faced with the same problems. The social contexts and means may differ from one country to another, but the objectives remain the same.

Policy objectives of the fight against Alzheimer's disease in Europe (OECD report, 2004)

To keep patients at home as long as possible and to push back admission into an institution
To provide help to caregivers so as to facilitate home support
To encourage patients to participate in their care for as long as possible
To coordinate services at local level
To promote equal treatment of needs
To facilitate early diagnosis

Our health system is an extremely complex organisation characterised by a host of structures combining a private and essentially outpatient medical system with a public, essentially hospital, system, together with different supervisory bodies for health and social aspects at local, regional and national level. This explains why public health policies are based on national plans relayed by regional plans. It is only these plans that can push forward and structure a "proactive" and consistent approach to a given disease or health problem, assuming that this disease or problem is considered a public health priority calling for concerted action so as to move closer to solving the problem posed. Lastly, an extra layer of complexity is added by the separation between the Ministry of Health and the Ministry of Research.

A first national plan entitled "Action Program for Persons suffering from Alzheimer's Disease and Related Diseases" was jointly launched by the Ministry of Health and Social Affairs and the Secretariat of State for the Elderly for the period 2001-2004. The plan included six major objectives:

- To identify the early symptoms and to give guidance
- To organise access to a diagnosis of quality
- To preserve personal dignity
- To support and inform the patients and their families
- To improve and reinforce accommodation facilities
- To encourage studies and clinical research

This initial plan led to the creation of the first Memory Resources and Research Centres (*Centres mémoire de Ressources et de Recherche (CMRR*)) at regional level and the Memory Consultations (*Consultations mémoire (CM*)) at a more local level. The plan was consolidated by the introduction of the Personal Autonomy Allowance (*Allocation personnalisée autonomie (APA*)) and the Local Centres of Gerontological Information and Coordination (*Centres locaux d'information et de coordination gérontologiques (CLIC*)).

Following on from this, a second national plan, entitled "Plan for Alzheimer's and Related Diseases" was launched for the period 2004-2007 under the auspices of the Ministry of Solidarity, Health and the Family and the Secretariat of State for the Elderly. This plan has ten objectives.

This second plan has improved the supply of care with the creation of 25 CMRRs, brought together in a National Federation, and 366 CMs linked in a network to the CMRRs. The aim of one CM per 15,000 inhabitants over the age of 75 is expected to be attained in 2007. Alzheimer's disease has been identified as a long-term illness, and a national ethical review on this pathology has been set in motion with the organisation of 5 national symposia. Substantial incentives and means have been allocated for the creation of health networks, day reception centres (15,500 places in 2007) and temporary accommodation facilities.

The ten objectives of the second national "Alzheimer Plan" (2004-2007)

To recognize Alzheimer's disease and related diseases as an illness its own right and to promote the respect of the ill person
To anticipate the needs of patients and families and to facilitate the matching of supply to needs
To facilitate early and quality diagnosis in order to slow down the development of the disease
To implement a reinforced policy of accompaniment for patients and their families at an early stage
To give better support to patients living at home
To adapt the accommodation facilities for the elderly in order to take the specific features of the disease into account
To develop the training of health care professionals and to help voluntary workers
To facilitate the care of patients in crisis situations
To take the specific characteristics of young patients into account
To encourage studies and clinical research

These first two plans have unquestionably helped us to take the measure of the phenomenon and to build up quality facilities throughout the country for improved care of the sick and for the purposes of evaluation. However, the plans overlooked the aggressive policy designed to encourage research into various aspects of Alzheimer's disease. It was not until 2007 that a "Neurosciences, neurology and psychiatry" invitation to tender was launched by the National Research Agency (*Agence nationale de la recherche (ANR)*), including an "Alzheimer's and related syndromes" component, plus an invitation to tender for "Longevity and Aging".

In addition, many problems have yet to be overcome, particularly with regard to: the early detection of the disease (which remains under-diagnosed and for which the diagnosis is made at too late a stage), patient follow-up due to lack of official recommendations for the assessment of needs in day hospitals and day care, clarification of the role of temporary accommodation facilities, residences and hospital establishments for dependent old persons (EHPADs).

In this latter sphere, the recent "Old Age Solidarity" plan should help to improve care in the EHPADs with the announced increase in the number of staff per patient, currently well below the ratio of 1 to 1 in France. The Opeps report on Alzheimer's disease and related syndromes (2005) made certain suggestions for improving the situation of patients and their families. Members of parliament and senators placed particular emphasis on three of these recommendations:

- Changing the image of the disease with the general public by means of information campaigns, particularly with a view to promoting faster detection and playing down the personal experience of the disease
- Helping general practitioners and coordinating the various aspects of care by the creation of a single contact, the "case manager", who would be responsible for health care coordination
- Giving a new impetus to clinical research and public health, without overlooking fundamental research, by launching an ambitious call for tenders covering all aspects of care for the disease

The government would seem to be following these recommendations since Alzheimer's disease was declared a "major national cause" in 2007. "Case manager" experiments are currently being carried out and will be submitted to evaluation. However, there is still a lack of coordination between staff in the health field and those active in the socio-medical sector.

Recommendations

Alzheimer's disease is often considered as an effect of the ageing process, but it is nonetheless a true pathology. This confusion partly explains why time has been lost in coming to terms with the disease.

The disease is characterised by specific brain damage revealed in neuropathology and resulting in the cognitive decline observed in the patients. Fundamental research in biology has given us an understanding of the major cellular and molecular mechanisms at the root of the deficiencies, and raised the possibility of new treatments sooner or later. The approach using the tools of neuropsychology has proved useful in describing the various levels of cognitive deficits. Finally, advances in brain imaging are an additional research asset in pinning down the structural and functional alterations, in addition to their contribution to diagnosis. At present, this diagnosis is usually made later or not even considered at all, despite the fact that medical and socio-medical care is important for exercising greater control over the development of the disease.

Scientific research has succeeded in separating Alzheimer's disease from the symptoms previously qualified as senile dementia, not the most edifying of terms. It is nevertheless true that the "biomedical" approach cannot be allowed to consider the patient only in terms of his or her brain. Studies in sociology, the humanities and social sciences have shown that the "personality" of the patient is maintained during his or her illness, and therefore social interactions with the family circle should be taken into account. Other people's opinion plays a part in the very conditions of the care given. If the deviation from the norm has major repercussions on social relations, then perhaps changing these norms may help to limit the stigma. A key objective is to change the image of this disease by making the general public and the medical profession better informed and more aware of what is involved.

The likely development of the disease in the coming years is enough to warrant a major overhaul in the organisation of medical, socio-medical and social care. Reviews and research are therefore essential in defining strategies that are properly geared to the full scale of the problem. Models (Appendix 3), which have been submitted to experiment in other countries, can serve as a point of departure for structuring prevention and care strategies at different stages of the disease. However, Alzheimer's disease is unusual in that its care presents particular difficulties at both the early and late stages of its development: at the time of its diagnosis (providing support for the patient and his/her family) and at the dependence phase when there are often several associated pathologies. The family doctor plays a key role in medical care but he must be backed up at the crucial stages and in emergency situations by specially trained personnel whose function is to coordinate all the procedures and the care to be implemented.

The commitment of the public authorities to the struggle against Alzheimer's disease may be gauged by their decision to declare the disease the "major national cause" of the year 2007. The recent announcement of an "Alzheimer plan" raises hopes that means commensurate with the challenge will be forthcoming, and opens up the prospect of an efficient coordination between fundamental research, clinical research, efforts in favour of patients and their families in tandem with patients' associations, and training for professional staff.

Following on from the analysis and synthesis of the scientific literature, the group of experts now puts forward a few non-exhaustive guidelines for initiatives in public health and

research. These proposals are based on acquired knowledge, the experience of expert-practitioners and the shortcomings and gaps highlighted in the course of the expert report. These proposals will naturally find their expression in the context of a national plan.

Better information and training

CHANGING THE IMAGE OF THE DISEASE IN THE GENERAL PUBLIC AND GETTING PEOPLE TO RECOGNIZE THE EARLY SYMPTOMS

The image of Alzheimer's disease in the general public is extremely negative, and is above all assimilated with fear; the diagnosis is perceived as a catastrophe and the patient as a passive individual. Meanwhile the family is left feeling completely helpless. In addition, the absence of a medicinal cure has the effect of turning patients and families away from medical consultations and sometimes discourages the doctors themselves. But it would be extremely detrimental if the disease was to be transformed into a "curse".

In order to improve the image of the disease, the group of experts recommends national information campaigns bringing together, for educational purposes, a few personalities concerned by or perhaps suffering from Alzheimer's disease (actors, journalists, etc.). These campaigns would help to extricate families from their isolation and draw attention to the services and care available to patients.

The group of experts also recommends that the public should be better informed and aware of the recognition of the first characteristic symptoms of the pathology (without causing alarm in the case of a perfectly harmless oversight). The aim is to establish an early diagnosis with the advantage of providing more appropriate and more effective care.

PROVIDING BETTER INFORMATION, TRAINING AND SUPPORT FOR DOCTORS AND HEALTH PROFESSIONALS, AND MAKING THEM MORE AWARE OF THE ISSUES INVOLVED

In the vast majority of cases, it is to the general practitioner that patients and their immediate family first turn when they are confronted by symptoms arousing suspicions of the disease. Amongst his patients, and according to the Sentinelles[14] network, each general practitioner in France treats, on average, five persons suffering from Alzheimer's disease, with one or two new cases per year. Doctors often feel powerless when faced with this kind of disease. They must be in a position to receive better information on the disease and its evolution. The elderly patient suffering from Alzheimer's disease is frequently polypathological (cardiovascular and pulmonary problems, diabetes, etc.). The therapeutic priorities are often established without taking Alzheimer's disease into account and care suffers as a consequence. Appropriate care will facilitate the observance of treatments and the therapeutic education of patients and their families. The group of experts recommends that, thanks to initial training, continuous training and information campaigns, doctors should be better prepared to organise global care of the person. In this connection, teaching could be improved by setting up a specialised national certification on Alzheimer's disease and the other forms of dementia. The national examination should include clinical cases of

[14] National health surveillance network comprising over 100 general practitioners in private practice covering the entire country and providing epidemiological data from their activity.

Alzheimer's disease. It is also vital that doctors should receive better training in communication skills, particularly with the patients themselves.

Recommendations emanating from the National Authority for Health and defining a line of conduct to follow will help doctors confronted with Alzheimer's disease. The group of experts recommends more actions in favour of general practitioners designed to give them more assistance and to make them more aware of their responsibilities with respect to the disease.

The group of experts also insists on the fact that a large number of professionals, whether local representatives, directors of retirement homes or personnel working in institutions for elderly dependents, are insufficiently informed of the specific features of Alzheimer's disease. It is urgent to raise awareness of the need to implement appropriate care.

ACCENTUATING AWARENESS OF THE NEED FOR A DIAGNOSIS

There is no reliable health indicator or register which could form the basis of an exhaustive and perennial census of cases of Alzheimer's disease in France. If no such data exist today, it is because the diagnosis is in many cases not made, even at the relatively severe stages of the disease. A study which does not include an active search of cases inevitably means that probably only cases diagnosed and treated by the health care system are taken into account, and the severe rather than the mild or moderate forms at that. Figures for persons living in institutions and for the very old are underestimated, principally because of diagnostic difficulties, and the same applies at the other end of the scale for younger persons.

On average, the diagnosis is made after 2.5 to 3 years of evolution and even later in patients under the age 65 years (for whom Alzheimer's disease is rarely suspected). Patients are not always aware of their disorders, and this constitutes an obstacle to diagnosis and care. A major European survey has shown that the average lapse of time between the first symptoms and diagnosis was 24 months in France, the longest interval after Great Britain, while the diagnosis is established earlier in Germany, Italy, Spain and Poland.

The group of experts recommends that all doctors should be encouraged to adopt a diagnostic procedure for Alzheimer's disease using a validated protocol. This would allow patients and their family circle to make the necessary arrangements and to adjust more easily to the situation (the appointment of a trustworthy person, assistance in managing the budget, evaluation of risks involved in driving a car, etc.).

An early diagnosis is justified if it transpires that medical, socio-medical and social care is useful for patient and family. It has been observed that the currently available medicinal drugs have some effect in slowing down the process of cognitive decline. However, the earlier the treatment is initiated the more effective it is. Moreover, other therapeutic or support measures are beneficial for both patient and family if they are introduced at the onset of the disease.

In spite of this, general practitioners in particular, and sometimes families, are not always convinced of the arguments in favour of care, especially the medicinal indications in Alzheimer's disease. The group of experts recommends that efforts should be made to make doctors and families more aware of the advantage of a diagnosis as soon as the first symptoms appear so that treatment and care adapted to each case can be introduced.

Improving the diagnosis and care of Alzheimers's disease and associated disorders

The efforts made in recent years have helped to reduce the wide regional disparities in terms of information structures, coordination, diagnosis, gerontological networks and socio-medical care of Alzheimer's disease. The transfer of new knowledge about the disease in the clinical field is expected to improve the provision of care throughout the country.

DEFINING A PROTOCOL ENABLING THE GENERAL PRACTITIONER TO CARRY OUT A PRELIMINARY EXAMINATION

Because the general practitioner is most often confronted with the patient's first complaints, the group of experts recommends that all general practitioners should, as soon as possible, have at their disposal a clearly defined protocol with which to make an initial assessment, using suitable and uncomplicated tools. The aim is to assess cognitive decline with, for example, the MMSE (*Mini Mental State Examination*), memory deficit, for example with the 5-word test, and impact on the daily life with, for example, the IADL (*Instrumental Activities of Daily Living*).

DEVELOPING THE USE OF NEUROPSYCHOLOGICAL TESTS AND IMAGING IN ORDER TO CONFIRM THE DIAGNOSIS

With regard to the analysis of the disease in its early stages, a neuropsychological assessment is indispensable for evaluating the deficient functions. This assessment requires the use of neuropsychological tools and behavioral scales, in particular to assess, in addition to episodic memory, semantic memory, executive functions and social cognition.

The group of experts stresses the pivotal role of professionals with specialist skills in neuropsychology in the diagnosis of the disease and the follow-up of patients. It encourages the recognition of neuropsychological skills (implying the need for specific training in neuropsychology and in the setting and interpretation of tests). Such recognition would contribute to a better functioning of memory consultations and of the consultations of private-practice specialists at local level (neurologists, psychiatrists, psychologists, geriatricians, speech therapists, etc.).

Brain imaging may help in the diagnosis. MRI identifies the morphological alterations that affect primarily the hippocampal region and then spread to the temporal neocortex, and finally throughout the associative cortex, in line with the regional distribution of neurofibrillary tangles. The group of experts recommends, for the purposes of diagnosis and the evaluation of a possible associated cerebral vascular pathology, an MRI exam for an analysis of atrophy in the hippocampus and the whole of the brain. This implies that practitioners are trained in reading qualitative data. In the future, quantitative analysis of the density of the grey matter in the whole of the brain or volume of certain important areas will be applied as a matter of routine. Finally, in cases where the diagnosis is open to doubt, the MRI exam should be repeated. It would seem necessary to standardize the procedure (orientation of sections, sequence, etc.). In situations where MRI is contraindicated (pace maker, claustrophobia, etc.), a scanner may be of use.

In the event of a difficult diagnosis, for example in the case of an atypical dementia, single photon emission computed tomography (SPECT), positron emission tomography (PET)

and/or the measurement of biomarkers in cerebrospinal fluid (amyloid β-peptide and tau protein) should be used.

DEVELOPING THE ORGANISATION OF CARE ADAPTED TO THE SPECIFIC PROBLEMS POSED BY ALZHEIMER'S DISEASE

In France, the "care itinerary" of patients suffering from Alzheimer's disease is complex: it varies according to individuals and where they live, with widely divergent modes of management and much inequality in the supply of care. The global care approach must take each individual's situation into account and should be adapted to his/her age, the stage of the disease, the associated disorders, the presence of any other pathologies and the patient's living conditions.

Alzheimer's disease can be regarded as a chronic disease for which various stages are defined (mild, moderate, severe). However, its evolution is not linear, varying between individuals and their environments. Some stages are particularly difficult to endure both for patients and their families. This is why care of the disease must be adapted; it can be broken down into different levels depending on the needs of patients.

The establishment of a consistent care management implies that once the diagnosis has been made, all patients with Alzheimer's disease must be accompanied throughout their illness and benefit from a follow-up defined by national recommendations (in terms of care and follow-up practices).

However, the group of experts draws attention to the fact that all patients, irrespective of the stage and severity of their condition, must be assisted, sometimes provisionally depending on the conditions, by a case manager. The case manager may intervene at different moments: difficulty in accepting the diagnosis, help in making decisions in everyday life (decision not to drive any more, assistance in keeping a budget, etc.), difficulties in care procedures, crisis situations, family malaise.

The case manager - for example, a nurse - is first and foremost a professional trained in Alzheimer's disease. The case manager is available, well accepted by the family and by the family doctor and has a good knowledge of all available resources. The case manager's role is to coordinate the care program in a personalised way, mobilising in turn the different resources in the light of the complexity of the situation, the social and family context and the various milestones facing both patient and family. This type of organisation has been set up on an experimental basis in several sites in France and is now being evaluated.

The group of experts recommends a coherent organisation of care, meeting the criteria for effectiveness and fairness. This organisation supposes a greater involvement on the part of general practitioners, a care package sufficient to prevent delays, better coordination with the private-practice neurologists, psychologists, speech therapists and with institutions such as Memory Resources and Research Centres (*Centres mémoire de Ressources et de Recherche (CMRR*)) and Memory Consultations (*Consultations mémoire (CM*)), whose activities should be supported. The group also emphasizes the important role that can be played by patient associations (France Alzheimer), especially in the early stages of the disease. Finally, the group of experts recommends the evaluation of the care organisation involving a "case manager" in the medical and welfare sectors throughout the population.

ADAPTING THE DETAILS OF MEDICINAL TREATMENT TO EACH CASE

The treatment and care objectives are not the same at different stages of the disease, and need to be redefined on a regular basis. At the mild and moderate stages, the aim is to stabilize the patient's state, if not to improve it, so as to postpone dependence as much as possible. At the later stages, when the patient has become very dependent, the principal objective is the patient's comfort and quality of life.

In France today, only 30% of patients with Alzheimer's disease are treated. Acetylcholinesterase inhibitors are indicated in the mild-to-moderate stages of Alzheimer's disease (score of between 10 and 26 inclusive on the MMSE scale) and memantine for the moderate-to-severe stages (score of between 19 and 3 inclusive on the same scale). After several studies, both these types of pharmacological treatment have shown a modest benefit on overall functioning and cognitive performance, together with low effectiveness on the associated neuropsychiatric symptoms. The question of whether they delay the evolution towards a more pejorative situation remains a matter for debate.

Once the diagnosis has been made, the group of experts recommends defining a care protocol based on the recommendations in force (HAS recommendations). The indication or discontinuation of pharmacological treatment, both in institutions and in an ambulatory situation, are based on an appropriate evaluation of the benefit/risk ratio at the individual level.

Alongside the pharmacological treatment, numerous non-medicinal approaches are available to patients suffering from Alzheimer's disease. However, they are applied very unevenly throughout the country. These techniques seek to optimize patient care by trying to improve different aspects of the disease: cognitive functioning, behavioral disorders, autonomy or well-being.

However, these treatments require a methodologically sound evaluation, with a sufficiently long follow-up and judgment criteria adapted to the objectives of the care. In the absence of the above, and in the meantime, the group of experts can for the time being recommend solely those approaches with a rational grounding, such as cognitive revalidation techniques and reminiscence therapy.

For ambulatory patients at the mild-to-moderate stages of the disease, the evaluation of their preserved cognitive abilities is recommended so that cognitive reinforcement work can focus on the available (rather than the deficient) abilities, and help them to develop compensatory mechanisms to overcome their difficulties in everyday activities. These non-medicinal care strategies nevertheless require the presence of professional staff with special training in Alzheimer's disease, and with expertise in such fields as neuropsychology, speech therapy, psychomotricity, ergotherapy, etc., backed up by a helper, depending on the patient's needs.

BETTER MANAGEMENT OF THE ASSOCIATED DISORDERS

As the disease progresses it is the associated non-cognitive disorders which will probably cause the most difficulties. Whether it is a question of neuropsychiatric symptoms (apathy, depression, agitation, sleep disorders, etc.) or gait and balance difficulties, non-cognitive symptoms speed up the evolution of the disease and the progression towards dependence. What is more, they increase the burden shouldered by the caregivers (spouse, children providing help in everyday life) and have an impact on the patient's quality of life. Finally, they constitute a major problem for the care teams in institutions. Here, the group of experts recommends improved training for the medical and supervisory teams in accommodation

sites (institutions and hospital establishments for dependent old persons – EHPADs) in the behavioral disorders associated with Alzheimer's disease.

Clinical practice has shown that the weight loss observed in the course of the disease is accompanied by a series of complications (alterations of the immune system, muscular atrophy, falls, fractures, dependence, etc.), giving rise to a worsening of the patient's health, recourse to emergency hospitalizations and an increased risk of institutionalization and mortality. The group of experts recommends the systematic screening of denutrition (easy-to-use tools are available) in the patient's initial evaluation and follow-up. The group recommends that weight loss should be combated by early diagnosis and increased calorie intake. However, the education of family helpers should not be overlooked as they can have a very positive role in nutritional care. Special advice geared to each case can considerably improve nutritional intake.

In general, the group of experts recommends the systematic evaluation of the symptoms linked to Alzheimer's disease, together with those related to another condition or an ill-adapted environment, starting at the earliest stages of the disease and continuing throughout its evolution. The group recommends the application of suitable treatments (both pharmacological and non-pharmacological) to the non-cognitive disorders associated with Alzheimer's disease, in accordance with the HAS recommendations, and in the context of the patient's global care.

DEVELOPING SUPPORT ACTIONS FOR CAREGIVERS

In France, it is still difficult to put a figure to the number of caregivers for persons suffering from Alzheimer's disease. The HID survey (Handicap-Disability-Dependence)[15], conducted in 1999, put the number of informal caregivers for persons aged 60 years and over at 3,700,000, without specifying the proportion of those persons with Alzheimer's disease. The caregivers are spouses in half of cases and children (or their spouses) in about one third of cases. Caregivers are aged on average 62 years and in 66% of cases are women. The number of hours of care given is greater than the number of hours of professional care, even in the case of heavy dependence.

The caregiver helps to make the care more effective by facilitating the patient's acceptance of this care. The caregiver also plays a decisive role in the recourse to professional assistance. The group of experts stresses the importance of taking into account the key role played by the caregiver in the application of medical and socio-medical care. However, in the case of persons recruited by the family or of home help, the question of their training is a major problem. The group of experts recommends that the home help facility should be professionalised.

There are frequent repercussions on the caregiver's mental health as a result of the help given to a patient suffering from dementia, with a high risk of depression (reported in 30% of cases), anxiety, sleep disorders (reported in 80% of cases), and increased consumption of psychotropic drugs. It is important to detect a heavy burden because it is a major determinant of a breakdown of home help leading to placement in an institution. The group of experts recommends a periodical assessment of the problems faced by caregivers at key moments such as the announcement of the diagnosis, the recourse to professional aid, the breakdown of home help, the patient's death, and the period following this death. The

[15] The results were obtained from a sample of 8800 persons aged 60 years and over and living at home in 1999.

consequences of aid on the caregiver's life can be evaluated through different dimensions (physical, psychological, socio-economic and financial). The experts call for the development and evaluation of strategies to support caregivers (stress management, coping[16], etc.). They also drew attention to the need to respond to urgent questions (provision of a telephone line).

The public authorities recognize the family as an essential resource. In 2002, the "Personal Autonomy Allowance" provided for the remuneration of non-qualified persons in return for the assistance given to dependent old persons. The "Solidarity Old Age" plan, introduced in June 2006, underlines the need to assist family caregivers, in particular by creating a right of respite or relief for them. Lastly, the Family Conference for the year 2006 threw its weight behind the objective of giving greater recognition, support and importance to the role of the family caregiver.

However, in the years ahead the "shortage" of natural caregivers is set to increase as a result of the socio-cultural changes already underway (reconstituted families, smaller families, women at work, children living further away, delegation of tasks) and changing lifestyles such as the professional activities of women. Bearing in mind demographical and sociological changes, new forms of care need to be envisaged whilst holding onto the family aid relationship. In this connection, the group of experts encourages the continued adaptation of the EHPADs to the care of Alzheimer patients and the development of special Alzheimer care units for persons presenting major behavioral disorders. Moreover, clinical practice reveals that a third of the patients attending memory consultations are aged under 75 years, and 10% under 60 years. The group of experts draws attention to the situation of these younger subjects for whom specific and adapted facilities must be created. In particular, the group recommends that special units should be developed in the establishments, or "therapeutic apartments" providing accommodation, in a specially adapted environment, for 5 to 10 persons supervised by properly trained health professionals, while at the same time preserving family ties.

ENCOURAGING PREVENTION

At the present time, the prevention of Alzheimer's disease is still an illusion. However, with the rapid growth of our knowledge, we can identify a few promising avenues of approach, including the impact of protective and risk factors.

Certain prevention factors liable to slow down the expression of the disease have already been identified: physical and intellectual activity, activities facilitating social interaction, certain dietary habits (consumption of fruit and vegetables, fish, olive oil, etc.), and the control of vascular risk factors, particularly high blood pressure. In the context of health promotion, the group of experts recommends information campaigns on the benefits of certain kinds of dietary behavior (in line with the recommendations of the National Health Nutrition Program), a healthy lifestyle (in particular physical activity) and the correction of vascular risk factors. All of these measures can help to prevent Alzheimer's disease.

[16] This describes the strategy by which the individual endeavours to adapt to a problem situation.

Promoting, developing and coordinating research in all its components

In the face of the major challenge to public health presented by Alzheimer's disease, promising areas of research must be sustained and supported, in particular by increased coordination between fundamental and clinical research, the development of research in health economics, the social sciences and humanities in order to gain a better understanding of the psychological and social aspects of the disease, and through the funding of extensive preventive trials.

The main objectives of fundamental research in Alzheimer's disease are to improve our understanding of the pathophysiological mechanisms involved and their consequences, so as to build up more effective therapeutic strategies and to perfect early diagnosis tools (biomarkers). Such objectives can only be attained by multidisciplinary and integrated research. To this end, the constitution of a network comprising a few regional centres of excellence, selected by international experts and combining complementary expertise in fundamental and clinical research, should prove extremely useful. Financial resources must be made available in order to support and strengthen these research laboratories (greater number of statutory, postdoctoral positions, creation of teams devoted to "Alzheimer Research", etc.) and to develop new platforms, particularly biological resource centres (tissue, plasma, spinal fluid banks, etc.) by means of support for specific calls for tender and by reinforcing regional involvement (for example, via the State-Region Project Contracts and the Research and Higher Education Poles).

As for clinical research, the main objectives are to identify risk and preventive factors linked to lifestyle, to evaluate the interest of early diagnosis and the various care mechanisms, particularly with regard to behavioral disorders. Clinical research also seeks to develop studies for improving the condition of caregivers, and cohort and economic studies designed to lay down intervention scenarios.

In the case of research in the fields of the social sciences and humanities, the principal objectives are to understand why Alzheimer's disease provokes such a negative image with the general public, policymakers and health care professionals. The research work must pin down the sociological elements that prevent policymakers from grasping the full magnitude of the problem, cause the general public to delay in seeking care and hinder long-term care on the part of doctors. The humanities must also contribute to the analysis and improvement of the quality of care, taking social differences into account, and to explaining why current facilities – such as support for caregivers – are not as successful as expected. The shortcomings of specialists in this field are obvious.

The CMRR network is a precious asset in facilitating translational research in the following missions: constitution of clinicopathological and epidemiological cohorts, validation of new markers, therapeutic trials, transfer of scientific innovations to personnel on site, continuous training of doctors and health personnel. It is therefore up to the CMRRs to attract and prompt local fundamental research designed to facilitate this transversality. Financial means must be forthcoming in order to consolidate existing cohorts and to analyse results (clinical research associates, technicians for biological resource centres, statisticians, etc.). The creation of a learned society dedicated to Alzheimer's disease would be an even greater help in developing exchanges between clinicians and researchers.

The group of experts suggests that the subjects sketched out above should be incorporated in the research development plan for Alzheimer's disease.

PROMOTING RESEARCH INTO THE CAUSES AND FACTORS OF THE DISEASE

The causes of Alzheimer's disease are not identified. The factors liable to favour its development are of the genetic, epigenetic and environmental kind. Their interaction thus determines a predisposition for developing the disease.

A genetic predisposition for Alzheimer's disease was quickly suspected if only because of the existence of monogenic family forms (less than 1% of cases). Three genes have been identified as responsible for these forms (*APP, PS1* and *PS2)*. However, their mutations do not explain all the monogenic forms. Current research strives to identify the genes responsible for the monogenic family forms by systematic family research, and the genes responsible for the forms without standard Mendelian transmission by constituting large independent case-control populations.

This kind of systematic research involves:
• The establishment of population biological data banks
• The development of high-speed genotyping tools (from several thousand to hundreds of thousands of polymorphisms)
• The understanding of the impact of genetic variations on the level of expression and activity of the protein in question
• The understanding of the role of genetic determinants on the pathophysiological processes by the use of experimental models

These research initiatives combine approaches in genomics, transcriptomics and proteomics, and use bioinformatic and biostatistical models.

The group of experts encourages research into the genetic aspect because it can contribute to a better understanding of the disease process and the description of new therapeutic targets. It may also provide a better understanding of the effectiveness of certain drugs (pharmacogenetics). Will a comprehensive knowledge of the genetic determinants of the disease lead to the elaboration of tools for early diagnosis or to the establishment of a risk scale which could be used in the prescription of a preventive treatment? This is a question that opens onto another debate.

The importance of epigenetic changes has not yet been properly tested, although powerful tools are now being introduced, for example for the systematic analysis of the level of DNA methylation in a healthy or pathological tissue. This is an area of research that needs to be developed for Alzheimer's disease.

Etiological epidemiological research in Alzheimer's disease is currently dominated by work on vascular risk factors with an increasing number of studies on nutrition, since many of these factors may be related to lifestyle. However, other avenues of inquiry, such as the place of medical history or exposure to certain environmental factors, should also be explored. The group of experts recommends further etiological epidemiological studies taking into account all the suspected risk factors and their interactions.

INTENSIFYING RESEARCH INTO MODIFIABLE RISK FACTORS AND DEVELOPING INTERVENTIONAL STUDIES

It is important to identify the risk and protection factors liable to modulate the duration of the long asymptomatic phase prior to the appearance of the disorders. Knowledge of these factors would facilitate action which may have important consequences in terms of public health: the ability to postpone the emergence of the disease, if only by a year, would save several billions of euros.

In cohort studies, many factors have been suggested, such as vascular risk factors, nutrition factors, medical history, and certain environmental factors. The risk factors that can lead to chronic diseases at advanced ages may have their origins in early periods of life and accumulate throughout it. We are therefore beginning to look more broadly at the subject's entire life, especially the period between the ages of 40 and 50 years.

The group of experts recommends further research relating to the identification of risk factors, especially those related to lifestyle, for a comprehensive approach to the subject requiring multidisciplinary teams.

Where there is a series of arguments suggesting the implication of certain factors in cognitive decline, the group of experts recommends that interventional studies be initiated on large samples. Examples include testing the usefulness of antihypertensive treatments or the care of diabetes. As for the factors associated with lifestyle, attention should be paid to nutritional factors by means of changes in eating habits or perhaps a dietary supplementation, to the promotion of physical, intellectual and cognitive activity, or to expanding or maintaining the social network.

The observational and interventional studies must be part of a medium or long-term financial outlook. The group of experts also recommends the use of existing French cohorts.

PROMOTING RESEARCH ON THE MECHANISMS OF THE DISORDERS IN ORDER TO FACILITATE THE DEVELOPMENT OF NEW TREATMENTS

Two major metabolic pathways are altered in Alzheimer's disease:

- The hyperphosphorylation of the tau proteins, which is responsible for a reduced axonal transportation within the neurons and leads to their degeneration. Neurofibrillary tangles are particularly observed in the internal temporal structures. These are affected at an early stage in Alzheimer's disease and their density is directly correlated with the severity of the dementia
- The abnormal production of amyloid-β peptide, proteic fragment released from the precursor of the amyloid protein (βAPP) through the action of two enzymes (β-secretase and γ-secretase). This peptide accumulates and is aggregated in the form of deposits or plaques known as "senile plaques". These plaques are constituted by accumulations of neuronal prolongations (dendrites and axons) in degeneration and whose centre is formed by extracellular deposits of amyloid peptide

Thus we today have a better knowledge of the biological cascade culminating in the appearance of the symptoms, and it is therefore possible to envisage blocking this cascade and hindering, or even stopping, the apparition of the symptoms although we do not yet know what causes the disease. Research is well advanced in this field and concerns the following targets:

- Blocking of the hyperphosphorylation of the tau protein by kinase inhibitors (GSK3, CDK5, etc.)
- Inhibition of the β- and γ-secretases by specific agents
- Disintegration of the amyloid deposits by selective antibodies either injected (passive immunization) or developed after injection of amyloid peptide (active immunization)

The group of experts recommends that work should continue on blocking the biological cascade which is responsible for the apparition of the cognitive decline of Alzheimer's disease. In particular, studies should be conducted in order to understand the synergy

between the two altered metabolic pathways, in relation with the neuronal death responsible for the clinical symptoms of the dementia.

More specifically, this work is based on the analysis of biological products (post mortem tissue, cerebrospinal fluid, plasma and serum) conditioned and preserved in biological resource centres, and the exploitation of experimental models using proteomics, structural biochemistry and cellular biology tools. This work makes it possible to consider the testing of new therapeutic approaches.

CONTINUING RESEARCH ON BIOMARKERS AND IN BRAIN IMAGING

The understanding of the mechanisms implicated in the etiopathogenesis of Alzheimer's disease has made it possible to identify biological markers of the disease. Measurements in the cerebrospinal fluid of three biomarkers are currently being explored in expert centres and specialised networks for help in diagnosing the disease: increase of total tau proteins and hyperphosphorylated tau proteins, and the reduction of fragment 1-42 of amyloid-β peptide. When the three parameters are modified, it would appear possible to predict the evolution towards dementia in patients suffering from mild cognitive disorders. But before this stage can be reached, other markers will have to be developed. The group of experts recommends that research should be continued into biomarkers useful for the predictive diagnosis of Alzheimer's disease by giving priority to those that can be measured in the peripheral blood.

The joint study of the morphological, metabolic and cognitive alterations in Alzheimer's disease at the pre-dementia stage is a method that has already yielded advances in the field of pathophysiology. This type of research must be continued. Some promising new methods of brain imaging have emerged. Thus PET molecular imaging highlights the accumulation of neurofibrillary degeneration and amyloid-β deposits by means of specific markers; diffusion tensor MRI studies the connectivity between the zones of the brain while functional MRI identifies the cerebral regions implicated in a given cognitive process or in the compensatory mechanisms. A joint imaging/neuropsychology approach can also be used in the context of therapeutic trials.

The group of experts recommends that research in brain imaging, particularly functional MRI or molecular imaging, should be encouraged, even though a routine application is difficult to conceive at the present time. Today, it is morphological imaging in MRI that is the most easy to apply. Its contribution is set to intensify thanks to the automation of image treatment techniques for visualising cerebral atrophy in regions that play a key role in the occurrence of cognitive disorders. Among the other methods, PET could play a crucial role at clinical level in the coming years, particularly in the case of difficult diagnoses.

The group of experts recommends that this work should be centered on highly specialised research centres in the field of neuropsychology, neuroimaging and biomarkers.

DEVELOPING CLINICAL RESEARCH IN ORDER TO EVALUATE THE MODALITIES OF EARLY DIAGNOSIS

Progress on the knowledge of the disease, on how to prevent the biological cascade and intervene on the associated factors, on the benefit of an early care and new therapeutic approaches that seek to slow down the disease – everything points in the same direction: the need to identify patients at the earliest possible date, as soon as the first symptoms appear. This clinical research is today focused on the following areas:

- The development of cognitive tests that are both sensitive and specific. In the area of episodic memory – whose deficits are at the heart of Alzheimer's disease – additional efforts must be made to evaluate all the dimensions of this memory (although there are relatively satisfactory tests for highlighting the difficulties in acquiring new information): the recall of personal memories, spatial and temporal context, prospective dimension, etc. Moreover, it is important to develop standardized tools evaluating other cognitive functions, quickly disrupted in Alzheimer's disease, such as semantic memory and executive functions. Finally, some areas of cognition, such as social cognition, must be further explored
- The development of objective scales on affective and behavioral disorders with good sensitivity right from the earliest stages, so that the evolution of the disorders can be evaluated when there are changes in the circumstances of life
- The evaluation of the use of biomarkers, directly related with the specific pathological process of Alzheimer's disease: increased concentrations of the tau protein and phosphorylated fragments, reduced concentration of amyloid peptide with the hope of taking measurements in the blood in the near future
- The evaluation of the routine application of quantitative analytical methods in standardized morphological (MRI) and functional (TEP) neuro-imaging

The group of experts recommends that this clinical research should be developed in close liaison with fundamental research. It also recommends that means should be made available in order to make progress in the early identification of the disease so that patients can benefit from new treatments long before the dementia stage. Finally, these means should contribute to the formation of the support network consisting of the regional clinical centres.

DEVELOPING RESEARCH IN ORDER TO EVALUATE THE DETAILS OF CARE AND IMPROVE THE PATIENTS' CONDITIONS OF LIFE

In the clinical sphere, the care team is confronted with the choice of medicinal drugs to prescribe in first intention, with the interest of a dual therapy or a change of medicine for the patient. The group of experts therefore encourages the development of strategic treatment trials, carried out independently at the initiative of the prescribers, in order to evaluate on clinically relevant criteria the modalities of use and the long-term efficacy of the available medicinal drugs.

The general practitioner is the special contact for the patient and his/her family, and is usually the person who records the first complaint emanating from the patient. The general practitioner makes the diagnosis or directs the patient to a specialised centre or professional for a complementary examination. Here, the group of experts recommends that a study should be carried out on the advantages and drawbacks of a systematic detection of the disease on the occasion of a general medical consultation according to a well-defined protocol. Similarly, the group recommends an evaluation of the impact of an initial prescription of the symptomatic treatments by the general practitioner.

Parallel to this pharmacological treatment, a wide variety of non-medicinal therapies are proposed to patients suffering from Alzheimer's disease in order to treat behavioral disorders. These disorders increase in frequency and severity as the disease develops, contributing to the loss of autonomy in everyday activities and accentuating the risk of dependence. Among those accommodated in EHPADs (hospital establishments for dependent old persons), 85% suffer from behavioral disorders, thus constituting a major problem for the care teams. However, the fact is that the non-pharmacological treatments

currently proposed for ambulatory and institutionalized patients are based on sound scientific proof. Consequently non-pharmacological care is very unevenly applied in France.

The group of experts recommends a rigorous and specific methodological evaluation of the non-pharmacological strategies applied to ambulatory patients, those residing in EHPADs and those accommodated in day centres or day hospitals.

DEVELOPING STUDIES FOR IMPROVING THE SITUATION OF THE HOME CAREGIVER

There is now general acknowledgement of the need to provide assistance, in different forms, to the home caregivers. However, this kind of intervention is rarely evaluated on a methodologically sound basis. The few studies published in this field have indicated, in certain cases, that the support programs for caretakers have proved beneficial in their ability to handle the patients' behavioral disorders and their placement in an institution.

The group of experts recommends that interventional studies should be developed with a view to studying the effect of services or support initiatives for caregivers on groups of target caregivers, taking into account their wide diversity (spouse, children, etc.). Help for caregivers must form part of the scope of these interventional studies which must therefore include judgement criteria for both patients and caregivers.

It is important to quantify this informal aid for patients suffering from Alzheimer's disease since demographic trends and socio-cultural changes are likely to lead to a reduction in this kind of aid which will have to be replaced, in large measure, by professional assistance.

EVALUATING THE PROBLEM OF PUBLIC HEALTH THROUGH PREVALENCE AND INCIDENCE DATA AND DEVELOPING COHORT STUDIES

Given the major public health problem and the cost to society posed by Alzheimer's disease, a precise knowledge of the prevalence in France and updated observational data are needed in order to define management policies and care. Repeated surveys will identify changes of frequency in the different age groups, particularly among subjects under the age of 65 years, over the age of 85 years and those in institutions. Estimates of the prevalence of dementia (including Alzheimer's disease) have been conducted using European data from the Euroderm group. The prevalence rate of dementia in patients above 65 years is estimated at 6.4%. In France, the number of patients involved is estimated at more than 850,000, with nearly 225,000 new cases each year in metropolitan France. Before 60 years, the prevalence is estimated at between 0.05 and 0.1%, i.e. about 32,000 patients in France. However, these figures remain very uncertain due to the lack of a reliable health indicator and a comprehensive census.

The group of experts recommends that no effort should be spared in obtaining as soon as possible reliable prevalence and incidence data according to age. This will make it possible to set out precise objectives for the care of this disease, as part of a coherent and consistent program. Such data are also essential if projections are to be made according to different hypotheses of intervention.

Studies on cohorts of patients or on subjects at risk as part of a longitudinal follow-up are necessary for the detection of risk factors, intervention projects on the same factors, validation of new criteria for early diagnosis, and the study of therapeutic efficacy (medicinal or otherwise) that can slow down the pathological process. These studies should incorporate biological resource centres together with the establishment of data bases, blood samples,

and, if possible, cerebrospinal fluid and post mortem samples that will accommodate the study of the prevalence of different types of brain lesions associated with Alzheimer's disease in the population.

At the same time, ongoing cohort studies in patients older than 65 years (Paquid, "3 Cités" study), and the existing French cohorts that have included subjects in the 40-50 age bracket (Suvimax, Gazel, E3N, etc.) constitute a resource that should be exploited.

DEVELOPING RESEARCH IN ECONOMICS IN ORDER TO DEFINE INTERVENTION SCENARIOS

The ageing of the population in industrialised countries is turning Alzheimer's disease into a serious economic problem. According to the Opeps report, the average annual cost per patient is estimated at around 22,000 €. Direct costs represent a total of approximately 10 billion euros, including nearly 10% of medical expenses (of which medicinal drugs account for less than 2% and socio-medical costs 90%). In 2004, expenditure was 12,146 € per family on average, whereas the average retirement pension for women was no more than 10,800 €.

Studies on cost-effectiveness designed to justify the prescription of new medicinal drugs, on the introduction of new forms of care or new care systems or policies, are limited in both number and quality. The group of experts recommends the development of such studies calculated to shed light on the decisions taken by policymakers, for example on the arbitration between home care and residential care, or on the economic interest of early diagnosis.

There is also a lack of economic studies on the behavior of those involved in dealing with the disease, whether families or health care teams. The economic strategies for coping with Alzheimer's disease, and the inter- and intra-generational transfers are seldom studied in a dynamic perspective which takes into account the income and capital of patient and family as well as the professional activity of the caregiver. The particularly difficult situation of those who find themselves just above the welfare thresholds must be taken into consideration in the analysis. The group of experts recommends work on the development of inter-generational solidarity, the future of socio-medical personnel and the implementation of the "case manager" in order to integrate these changes in the scenarios produced. The group recommends studies dealing with the economic consequences, even the effectiveness, of the different forms of support proposed to the caregivers (relief, exemption from social security contributions, tax exemption, etc.). The economic management of crisis episodes by the various parties concerned deserves some attention inasmuch as it takes up a considerable amount of resources.

There are no studies showing, for example, patients' selection criteria in the different care structures, the method of pricing, the economic management of care pathways theoretically adapted to Alzheimer's disease. The group of experts recommends the longitudinal follow-up of patient cohorts for a better knowledge of the different components of care and the costs associated with each component. It is important that extensions targeting Alzheimer's disease should be added to recent economic work concerning scenarios for financing dependence.

DEVELOPING RESEARCH IN SOCIOLOGY, THE HUMANITIES AND THE SOCIAL SCIENCES IN ORDER TO IMPROVE ACCEPTANCE OF THE DISEASE BY SOCIETY

Sociology does not feature prominently as far as research in the field of Alzheimer's disease is concerned. In such studies as do exist, it is the experience of the disease that is most often treated by sociology (or social psychology).

The patients themselves, in their ability to manage their life as ill people, in terms both of difficulties and resources, are conspicuous by their absence from this research. The sociological work carried out in English-speaking countries shows that studies on the experience of the disease are possible; French sociology also possesses the theoretical tools for meeting this kind of demand. The question of how to measure the patient's quality of life must be posed at an interdisciplinary level (sociology, psychology, medicine, etc.).

The group of experts recommends studies on the patients' trajectory, from the pronouncement of the diagnosis and the way it is received right through to the conditions pertaining at the end of the patient's life. The "exogenous" representations of the disease – that is to say, the way it is perceived by others – which run the gamut up to stigmatisation, must be studied from the point of view of their role in the patient's management of his/her illness. Precise research must be conducted into the interaction between patient, members of the family (in particular caregivers), the neighbourhood and socio-medical professionals, so that a better understanding can be reached of the requirements for professional services, and in particular of the quality of these services.

There is every reason to think that sociological criteria go a long way towards explaining the fact that only half of the patients are diagnosed, and that only a part of these patients actually receive a treatment. The group of experts recommends studies that measure (and help us to understand) the differences in access to diagnosis, treatment and social care in terms of gender, social category and geographical location.

Case monographs would be very useful for the purposes of comparison. It is important to evaluate the patient's global situation, socially characterised in his/her living environment (in the context of a precise supply of services) if we are to understand these inequalities, particularly those of a geographical nature. For this body of research, the group of experts recommends an interdisciplinary cooperation (sociology, economics, geography, epidemiology).

Appendix

APPENDIX 1

Inserm collective expert review

Methodology

An Inserm collective expert review[2] sheds scientific light on a given subject in the field of health on the basis of a critical analysis and synthesis of the international scientific literature. The expert reviews are implemented at the request of institutions wishing for access to recent research data pertinent to their decision-making process with respect to public policy. An Inserm collective expert review is to be considered as an initial stage that is necessary but most frequently not sufficient to result in decision-making. The conclusions of the collective expert review contribute to, but cannot replace, debate between the professionals involved or society debate if the questions addressed are particularly complex and sensitive.

At the request of an institution, the Inserm collective expert review may be accompanied by an 'operational' expert review addressing application of the knowledge and recommendations and taking into account contextual factors (existing programs, structures, players, training, etc.). The latter type of expert review elicits contributions from the players in the field able to respond to the feasibility aspects, representatives of the administrations or institutions responsible for promoting applications in the field involved, experts having contributed to the reviews, and representatives of patient associations. The sharing of varied cultures and experience enables a complementary approach to the collective expert review in an operational framework. Moreover, a variety of work (recommendations for good practices, public hearings, etc.) implemented under the auspices of the High Authority for Health (HAS) may follow an Inserm collective expert review.

Collective expert review has been an Inserm mission since 1994. Some sixty collective expert reviews have been implemented in numerous health fields. The Institute guarantees the conditions under which the expert review is implemented (exhaustiveness of the document sources, qualification and independence of the experts, transparency of the process).

The Inserm Center for Collective Expert Reviews organizes the various stages of collective expert review from the initial problem statement through to communication of the report, with the assistance of Inserm departments. The Center team, consisting of engineers, researchers and a secretariat, implements the document searches, logistics and chairing of the expert review meetings. The team contributes to the scientific writing and to compiling the expert review products. Regular exchanges with other public organizations (EPST) implementing the same type of collective expert review have enabled similar procedures to be set up.

Problem statement

The problem statement phase enables definition of the institution's request, checking that accessible scientific literature on the issue raised is available and drawing up specifications which state the framework of the expert review (status report on the perimeter and main themes of the subject), its duration and budget, documented by a convention signed by the sponsor and Inserm.

[2] Inserm accredited label

During the problem statement phase, Inserm also organizes meetings with patient associations in order to ascertain the questions those associations wish to have addressed and the data sources available to them. The information is incorporated in the scientific program of the expert review. For certain subjects, exchanges with industrial partners are indispensable in order to obtain access to complementary data not available in the databases.

Expert review monitoring committee and assistance unit setup

A monitoring committee consisting of the institution and Inserm representatives is set up. The committee meets several times during the expert review to monitor the progress of the review, discuss any difficulties encountered in addressing the issues, ensure compliance with the specifications and examine any new factors in the regulatory and political context pertinent to the ongoing review. The committee also meets at the end of the expert review for presentation of the conclusions and prior to compilation of the final version of the report.

For expert reviews addressing sensitive issues, an assistance unit is also set up and consists in representatives of the Directorate General of Inserm, scientific board, ethical committee of Inserm, communication department, human and social science researchers and specialists in the history of science. The role of that unit is to identify, at the start of the expert review, the issues liable to have strong resonance for the professionals involved and civil society, and to suggest hearings of professionals in related fields, representatives of civil society and patient associations. In short, the unit is responsible for measuring the perception that the various recipients may have of the expert review. Before publication of the expert review report, the assistance unit pays special attention to the wording of the synthesis and recommendations, including, if necessary, the expression of the various points of view. Downstream of the expert review, the unit is responsible for strengthening and enhancing the circulation of the results of the expert review, for instance by holding colloquia or seminars with the professionals of the field and players involved or holding public debates with representatives of civil society. Those exchanges are to ensure enhanced understanding and adoption of the knowledge generated by the expert review.

Literature searching

The specifications drawn up with the institution are translated into an exhaustive list of scientific questions reflecting the perimeter of the expert review with the assistance of referral scientists in the field and members of Inserm. The scientific questions enable identification of the disciplines involved and construction of a key-word arborescence employed in the systematic searching of international biomedical databases. The articles and documents selected on the basis of their pertinence with respect to answering the scientific questions constitute the document base, which is forwarded to the experts. Each member of the group is asked to add to the document base over the course of the expert review.

Institutional reports (parliamentary, European, international, etc.), raw statistical data, associations' publications and other documents from the gray literature are also inventoried (non-exhaustive) in order to complement the academic publications provided to the experts. The experts are responsible for taking or not taking into account those sources depending on the interest and the quality of the information supplied. Lastly, a review of the main articles in the French press is supplied to the experts during the expert review in order to enable them to follow developments on the theme and the social repercussions.

Constitution of the expert group

The expert group is formed on the basis of the scientific skills necessary for analysis of the bibliography collected and on the basis of the complementarity of the group members' approaches. Since an Inserm collective expert review is defined as a critical analysis of the academic knowledge available, the choice of the experts is based on their scientific skills certified by publications in peer-review journals and their recognition by their peers. The expert recruitment logic, based on scientific

skills and not on knowledge in the field, is to be stressed in that it is a frequent source of misunderstandings when the expert reviews are published.

The experts are selected from the French and international scientific community. They are to be independent of the partner sponsoring the expert review and recognized pressure groups. The composition of the expert group is validated by the Directorate General of Inserm.

Several scientists outside of the group may be requested to contribute occasionally to a particular theme during the expert review.

Expert review implementation lasts between 12 and 18 months, depending on the volume of literature to be reviewed and analyzed and the complexity of the subject.

Initial expert group meeting

Before the first meeting, the experts receive a document explaining their mission, the scientific program (issues to be addressed), schedule, the expert review bibliographic database to date and articles more specifically addressing certain experts on the basis of the skills.

During the first meeting, the expert group discusses the list of issues to be reviewed and completes or modifies it. The group also examines the document base and proposes supplementary searches with a view to enriching that base.

Expert critical analysis of the literature

During the meetings, each expert orally presents a critical analysis of the literature with respect to the aspect allocated to the expert in his/her field of expertise and communicates the accepted facts, uncertainties and controversies with respect to current knowledge. The questions, remarks and points of convergence or divergence elicited by the group analysis are taken into consideration in the section that each of the experts compiles. The analysis report, consisting of various sections, thus constitutes the state of the art for the various disciplines pertinent to the issue under review. The bibliographic references used by the expert are cited in and at the end of each section.

Synthesis and recommendations

The synthesis summarizes the broad lines of the literature analysis and identifies the main findings and principles. Contributions from contributors outside the group may be summarized in the synthesis.

The synthesis is more specifically intended for the institution and decision-makers with a view to use of the knowledge presented therein. The wording of the synthesis is to take into account the fact that it will be read by non-scientists.

As of report publication, the synthesis is posted on Inserm's website. The synthesis is translated into English and posted on the NCBI/NLM site (National Center for Biotechnology Information of the National Library of Medicine) and Sinapse site (Scientific INformAtion for Policy Support in Europe, European Commission site).

If requested by the institution, certain collective expert reviews include 'recommendations'. Two types of 'recommendations' are formulated by the experts group. 'Principles for action' based on a validated scientific reference system with a view to defining future public health action (mainly in screening, prevention and management) but which are not under any circumstances to be considered 'operational' recommendations insofar as no economic or political components have been taken into account in the scientific analysis. 'Research orientations' are also proposed by the experts group with a view to filling in the gaps in scientific knowledge observed during the analysis. Once again, these proposals cannot be considered 'priority' research without their being put into perspective. That is the task of the pertinent authorities.

Critical review of the report and synthesis by prominent 'readers'

For certain expert reviews addressing sensitive subjects, a critical reading memorandum is requested from several prominent 'readers' selected on the basis of the scientific or medical knowledge and managing or evaluating French or European research programs or having contributed to ministerial working groups. Similarly, the report and synthesis (and recommendations) may be submitted to figures with good knowledge of the 'field' and able to grasp the socioeconomic and political issues associated with the knowledge (and proposals) presented in the expert review.

Presentation of the conclusions of the expert review and debate

A seminar open to the various sectors involved in the subject of the expert review (patient associations, professional associations, unions, institutions, etc.) enables an initial debate on the conclusions of the expert review. On the basis of that exchange, the final version of the synthesis document incorporating the various viewpoints expressed is compiled.

APPENDIX 2

Diagnostic criteria of Alzheimer's disease according to ICD-10 (World Health Organisation, 1993)

A-	Presence of dementia
B-	Insidious onset and slowly progressive deterioration It is usually difficult to detect the onset of disorders and the patient's entourage sometimes becomes suddenly aware of the presence of a deterioration An apparent plateau may occur in the progression
C-	Absence of argument, following the clinical examination and complementary investigations, to suggest that the mental state may be due to other systemic or brain disease which can induce a dementia (e.g. hypothyroidism, hypercalcemia, vitamin B12 deficiency, nicotinic acid deficiency, neurosyphilis, normal pressure hydrocephalus or subdural hematoma.)
D-	Non-sudden onset and absence, at an early stage of the evolution, of neurological signs of focal damage, e.g. hemiparesis, sensory loss, visual field defects or a lack of coordination (these manifestations may, however, be added secondarily)

Diagnostic criteria of Alzheimer's disease according to DSM-IV (American Psychiatric Association, 1994)

A. The development of multiple cognitive deficits manifested by both:
Memory impairment (impaired ability to learn new information or to recall previously learned information)
One or more of the following cognitive disturbances:
Aphasia (language disturbance)
Apraxia (impaired ability to carry out motor activities despite intact motor functions)
Agnosia (failure to recognize or identify objects despite intact sensory functions)
Disturbances in executive functioning (ie planning, organizing, sequencing, abstracting)

B. The cognitive deficits in criteria A1 and A2 each cause significant impairment in social or occupational functioning and represent a significant decline from a previous level of functioning

C. The course is characterized by gradual onset and continuing cognitive decline

D. The cognitive deficits of criteria A1 and A2 are not due to any of the following:
   1) other central nervous system conditions that cause progressive deficits in memory and cognition (e.g. cerebrovascular disease, Parkinson's disease, Huntington's disease, subdural hematoma, normal pressure hydrocephalus, brain tumour)
   2) systemic conditions that are known to cause to dementia (e.g. hypothyroidism, vitamin B12 or folate acid deficiency, niacin deficiency, hypercalcemia, neurosyphilis, HIV infection)
   3) substance-induced conditions

E. The deficits do not occur exclusively during the course of a delirium

F. The disturbance is not better accounted for by another Axis I disorder (e.g. major depressive disorder, schizophrenia)

Diagnostic criteria of Alzheimer's disease according to NINCDS-ADRA (McKhann, 1984)

I The criteria for the clinical diagnosis of probable Alzheimer's disease include:

- dementia established by clinical examination and documented by the Mini-Mental Test (Folstein, 1975), the Blessed Dementia Scale (Blessed, 1968) or some similar examination, and confirmed by neuropsychological test;
- deficits in two or more areas of cognition;
- progressive worsening of memory and other cognitive functions
- no disturbance of consciousness;
- onset between ages 40 and 90, most often after age 65; and
- absence of systemic disorders or other brain diseases that in and of themselves could account for the progressive deficits in memory and cognition.

II The diagnosis of probable Alzheimer's disease is supported by:

- Progressive deterioration of specific cognitive functions such as language (aphasia), motor skills (apraxia), and perception (agnosia);
- Impaired activities of daily living and altered patterns of behavior;
- Family history of similar disorders, particularly if confirmed neuropathologically; and
- Laboratory results of:
- Normal lumbar puncture as evaluated by standard techniques,
- Normal pattern or nonspecific changes in EEG, such as increased slow-wave activity, and
- Evidence of cerebral atrophy on CT with progression documented by serial observation.

III Other clinical feature consistent with the diagnosis of probable Alzheimer's disease, after exclusion of causes of dementia other than Alzheimer's disease, include:

- Plateaus in the course of progression of the illness;
- Associated symptoms of depression, insomnia, incontinence, delusions, illusions, hallucinations, catastrophic verbal, emotional, or physical outbursts, sexual disorders, and weight loss;
- Other neurologic abnormalities in some patients, especially with more advanced disease and including motor signs such as increased muscle tone, myoclonus, or gait disorder;
- Seizures in advanced disease; and
- CT normal for age.

IV Features that make the diagnosis of probable Alzheimer's disease uncertain or unlikely include:

- Sudden, apoplectic onset;
- Focal neurologic findings such as hemiparesis, sensory loss, visual field deficits, and incoordination early in the course of the illness; and
- Seizures or gait disturbances at the onset or very early in the course of the illness.

V Clinical diagnosis of possible Alzheimer's disease:

- May be made on the basis of the dementia syndrome in the absence of other neurologic, psychiatric or systemic disorders sufficient to cause dementia, and in the presence of variations in the onset, in the presentation, or in the clinical course;
- May be made in the presence of a second systemic or brain disorder sufficient to produce dementia, which is not considered to be the cause of the dementia; and
- Should be used in research studies when a single, gradually progressive severe cognitive deficit is identified in the absence of other identifiable cause.

VI Criteria for diagnosis of definite Alzheimer's disease are:

- The clinical criteria for probable Alzheimer's disease and
- Histopathologic evidence obtained from a biopsy or autopsy.

VII Classification of Alzheimer's disease for research purposes should specify features that may differentiate subtypes of the disorder, such as:

- Familial occurrence;
- Onset before age of 35;
- Presence of trisomy 21; and
- Coexistence of other relevant conditions such as Parkinson's disease.

Proposed new diagnostic criteria for probable Alzheimer's disease (Dubois et coll., 2007)

Diagnostic criteria for AD

Probable AD: A plus one or more supportive features B, C, D, or E

Core diagnostic criteria

A. Presence of an early and significant episodic memory impairment that includes the following features:

1. Gradual and progressive change in memory function reported by patients or informants over more than 6 months

2. Objective evidence of significantly impaired episodic memory on testing: this generally consists of recall deficit that does not improve significantly or does not normalise with cueing or recognition testing and after effective encoding of information has been previously controlled

3. The episodic memory impairment can be isolated or associated with other cognitive changes at the onset of AD or as AD advances

Supportive features

B. Presence of medial temporal lobe atrophy

• Volume loss of hippocampi, entorhinal cortex, amygdala evidenced on MRI with qualitative ratings using visual scoring (referenced to well characterised population with age norms) or quantitative volumetry of regions of interest (referenced to well characterised population with age norms)

C. Abnormal cerebrospinal fluid biomarker

• Low amyloid β_{1-42} concentrations, increased total tau concentrations, or increased phospho-tau concentrations, or combinations of the three

• Other well validated markers to be discovered in the future

D. Specific pattern on functional neuroimaging with PET

• Reduced glucose metabolism in bilateral temporal parietal regions

• Other well validated ligands, including those that foreseeably will emerge such as Pittsburg compound B or FDDNP

E. Proven AD autosomal dominant mutation within the immediate family

Exclusion criteria

History

• Sudden onset

• Early occurrence of the following symptoms: gait disturbances, seizures, behavioural changes

Clinical features

• Focal neurological features including hemiparesis, sensory loss, visual field deficits

• Early extrapyramidal signs

Other medical disorders severe enough to account for memory and related symptoms

• Non-AD dementia

• Major depression

• Cerebrovascular disease

• Toxic and metabolic abnormalities, all of which may require specific investigations

• MRI FLAIR or T2 signal abnormalities in the medial temporal lobe that are consistent with infectious or vascular insults

Criteria for definite AD

AD is considered definite if the following are present:

• Both clinical and histopathological (brain biopsy or autopsy) evidence of the disease, as required by the NIA-Reagan criteria for the post-mortem diagnosis of AD; criteria must both be present

• Both clinical and genetic evidence (mutation on chromosome 1, 14, or 21) of AD; criteria must both be present

APPENDIX 3

Care models prioritised in function of patients' needs

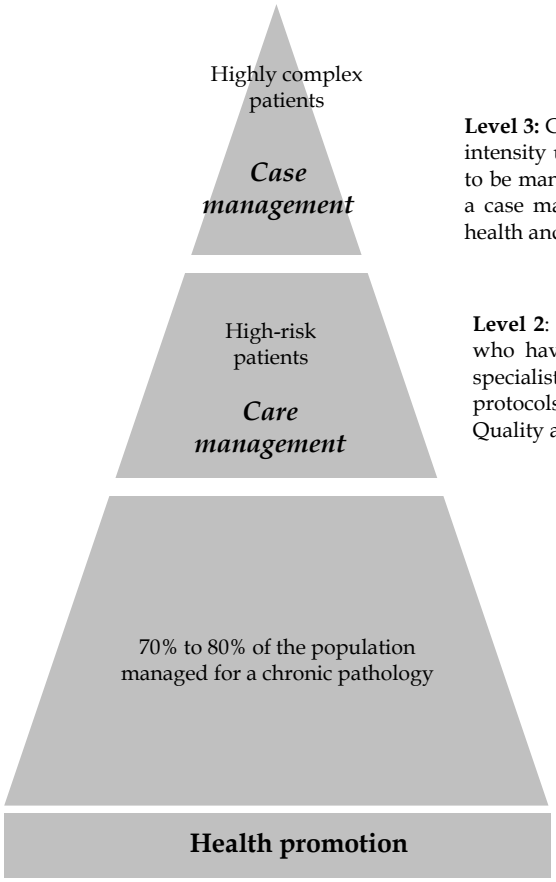
As part of their general policy of managed care, different countries, including the United States, Germany and England, have experimented with a hierarchical organisation, based on different models advocating a coordinated and proportionate approach to the needs of patients. These models are represented in the form of a pyramid whose base consists of health promotion actions and whose apex is the future management of care for patients presenting the maximum degree of risk.

The National Health Service (NHS) in the UK has applied this kind of approach to the management of care for patients suffering from chronic diseases (Figure 1).

This national care model, which progressively involves *care/disease managers* and *case managers* depending on the specific needs of patients, has been designed to encourage a transfer of care from hospitals to primary health services and the general practitioner, relying as much as possible on social and associative intervention.

In France, this type of organisation has recently given rise to a debate and review initiated by the Inspectorate-General of Social Affairs of Social Affairs (*Inspection générale des affaires sociales* - Igas) to improve the care of the chronically ill, and whose findings have been set out in a report published in September 2006[18]

[18] Report RM2006-136P presented by Pierre-Louis Bras, Gilles Duhamel and Etienne Gras (IGAS, 2006).



Level 3: Case management - requires the identification of the very high intensity users of unplanned secondary care. Care for these patients is to be managed using a community matron or other professional using a case management approach, to anticipate, co-ordinate and join up health and social care.

Level 2: Disease-specific care management - This involves providing people who have a complex single need or multiple conditions with responsive, specialist services using multi-disciplinary teams and disease-specific protocols and pathways, such as the National Service Frameworks and Quality and Outcomes Framework.

Level 1: Supported self care - collaboratively helping individuals and their carers to develop the knowledge, skills and confidence to care for themselves and their condition effectively.

Figure 1: National Health Service (NHS) "Population Management" intervention model

Source: http://www.dh.gov.uk/en/Policyandguidance/Healthandsocialcaretopics/longtermconditions/DH_4130652