

Alzheimer's disease: when the mind goes astray



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Alzheimer's disease (AD) is the most common mental disorder amongst elderly people, and one that continues to puzzle the scientific community. And for good reason: its cause is still unknown. Though a number of symptoms can be alleviated, the disease still cannot be checked in its course. However, new therapies may be developed in the near future. Various drugs now available appear to focus on one source only: proteins. The amyloid- β protein is foremost yet it is far from the only one responsible for the fatal outcome of AD.

18 million people are afflicted with some kind of dementia worldwide. The World Health Organization (WHO) defines such pathologies as a gradual decline of memory, reasoning power and personality. Several types of mental disorder - referred to as senile insanity - develop at an advanced age. More than half the cases are caused by AD. In Switzerland alone, 90'000 patients suffer from a form of dementia. In Europe, 5% of the population between the age of 70 and 74 are at risk; for those over 85, the risk is 20%. In the US, about 5% of the population aged between 65 and 74 develop AD, and about 1 person in 2 are afflicted when over 85. Unfortunately, this is only the beginning. According to experts, by 2025 some 34 million people will have succumbed to AD or some other mental disturbance. Such an estimate is directly linked to another observation, every bit as breathtaking: in our wealthy part of the world, the population is inexorably growing older. According to the United Nations Population Fund, this is a trend which will spread throughout the world, and by 2050 the proportion of people over the age of 65 will have doubled.

Personality breakdown

There are two forms of AD. The most common form affects people, at random, over the age of 70. The second form is hereditary and far more rare, representing barely 5% of all AD patients. It is handed down through generations of one family and is therefore known as the "family" form of the disease. It can develop as early as the age of 30 but most cases arise around the age of 40. Very often, and especially in the event of non-hereditary AD, the illness is difficult not only to diagnose with precision but also to know when it begins since early symptoms are so similar to the first signs of the normal ageing process of the brain.

It all starts with small failings of the memory such as mild forgetfulness that can be bothersome in every day living, or words that will not come to mind. Recent events have no hold on the memory. Answers to questions such as "What did you have for supper last night?" remain vague. On the other hand, memories of old are preserved far longer.

Memory, however, is not the only cognitive faculty¹ to be affected. Concentration and attentiveness diminish gradually and it becomes more and more difficult to follow a conversation with more than one person. Language is slowly impoverished. Additional disorders are the inability to reflect in a coordinate manner, to make judgments or even to orientate oneself in space or time. Little by little, patients lose their capacity to recognize objects or even familiar faces. Progressively, patients lose their self-sufficiency to such an extent, that simple actions such as lighting a candle, eating or dressing become impossible.

Patients also present a series of symptoms that can be very difficult to put up with for those living with them. At the outbreak of the illness, they frequently become listless, demonstrating a lack of interest, impassiveness and loss of initiative. They become unsociable, often irritable, anxious, depressed or restless; they sometimes suffer from hallucinations and, in the end, their behavior and personality are deeply affected. The illness follows its course for a period of 8 to 12 years. Currently, there is no curative therapy and patients usually succumb to complications such as undernourishment or thrombosis due to lack of exercise.

One disease, thousands of proteins

It was the autopsy of a female patient in 1906, known as August D., which brought to light this devastating illness. Alois Alzheimer, a German neuropsychiatrist who treated her from 1901 to 1906, was the first to record the clinical descriptions of this mental disorder which was to take his name. On her death, Alois Alzheimer examined his patient's brain. He noted an atrophy which later was recognized as being a large number of destroyed nerve cells and he identified the two lesions that are characteristic of what was to be known as AD: senile plaques and neurofibrillar degeneration (ND). Senile plaques take on the appearance of flat pastilles of proteins aggregated between the brain cells whereas ND resembles strings of proteins within the neurons themselves.

These lesions are brought about by the action of many proteins, three of which drew the attention of scientists after discovering hereditary cases of AD: the amyloid protein and presenilins 1 and 2. Genes containing the "recipe" for these proteins may present irregularities, also called mutations. These irregularities are then transmitted from

generation to generation and the carrier of a mutation in any one of these three genes will unfortunately succumb to the disease. Consequently, it was essential to investigate further to understand the role of these proteins in the evolution of AD.

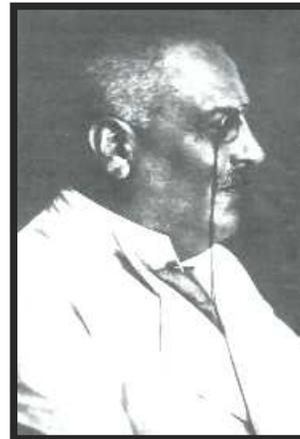


Fig.1 Alois Alzheimer (1864-1915).

Spotlight on the platelets

The amyloid protein and presenilins 1 and 2 play a central part in the appearance of the senile plaques. This lesion, typical of all types of AD, is the result of the excessive accumulation of a key element between cells: the β -amyloid fragment (β A). β A is the truncated form of the amyloid protein. The latter, whose role is not yet well defined, is found in various cells of our organism and especially in the membrane of neurons.

How then is the β A fragment released into the brain? The amyloid protein is systematically split into several fragments, each of which seems to offer some kind of protection to the neurons. This splitting-up of the protein is controlled by the presenilins - amongst others. One of these amyloid fragments, however, is toxic and can change its shape into a folded structure termed a " β sheet", thus becoming a β -amyloid. This insoluble and "indestructible" fragment causes aggregates to form and which become the core of the senile plaques.

The deposits of β -amyloid seem in many ways to be detrimental to the neurons and there can be no doubt that they gradually threaten their very existence. The brain then retaliates with the help of our immune system, which delegates cells to the plaques seemingly to destroy the β -amyloid fragments. Only these same cells help produce free radicals that are detrimental to the neurons' survival, so they only add to the toxic effect of the plaques.

¹ The process by which we acquire, organize and use information and knowledge constitutes our cognitive faculties.

Strings of proteins

The loss of neurons in AD is probably mainly due to ND. Unlike the senile plaques which operate on the surface of the neurons, ND operates inside them. The tau protein is at the root of these internal disruptions. Tau protein's customary role is closely associated with a group of protein cylinders, known as microtubules, which it helps to assemble. The specific architecture of these microtubules gives the cell its shape, much in the way that bones shape a body. Microtubules also serve as a means of transport for nutrients and other molecules inside the cell. However, for a reason which remains unclear, everything goes

wrong if the tau protein becomes defective. It loses its affinity for the microtubules, which then disintegrate. Consequently, the cell is deformed. Moreover, the irregular tau proteins cling together forming the strings which are so typical of this kind of lesion. And that is not all. The disintegration of the microtubules spells the loss of transport routes towards the cellular prolongations of the neurons, i.e. the axon and the dendrites, which are at the heart of neuron transmission. As a result, the neurons function badly and finally disappear.

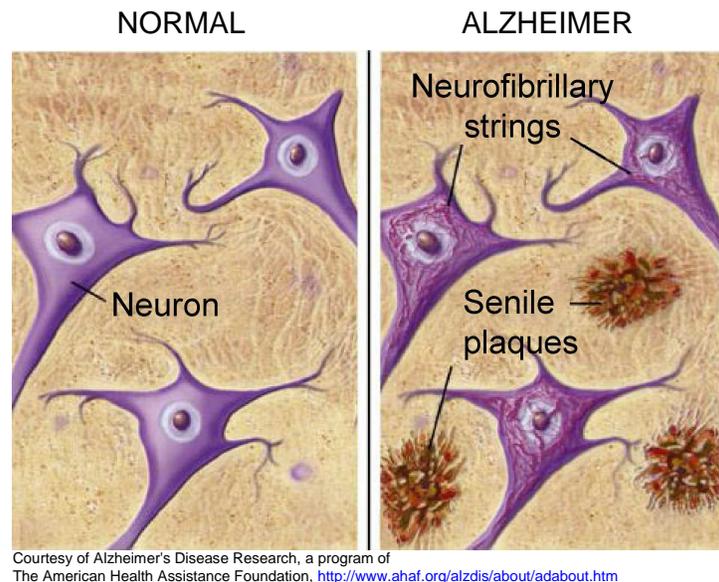


Fig.2 Lesions caused by AD. Neurofibrillar degeneration is characterized by "strings" of tau proteins inside the neurons, and the senile plaques by β -amyloid deposits which appear as flat "pastilles" situated in between the cells.

The memory network

The glutamatergic and the cholinergic neurons are particularly weakened in the lesions caused by AD. Glutamate and acetylcholine, which give their name to these neurons, are small molecules essential to neuron communication: the neurotransmitters. Information is transferred from one neuron to another across structures known as synapses. A neuron sends a nerve impulse along its axon. Once the impulse has reached the synapse, neurotransmitters are released, which in turn will transfer the message to the neighboring neuron. The latter traps the neurotransmitters thanks to a number of receptors on its surface. The nerve impulse is then propagated along this second neuron to the next synapse. And so on. Furthermore, one neuron is connected not to one but to many neurons, and together they form several networks.

In the cortex and the hippocampus, different zones related to the processes of learning and memory - both of which are targets of AD - harbor cholinergic and glutamatergic neurons. It seems that the stuff of memory is elaborated at the center of the neuronal networks. Like clay, these networks are malleable and adapt, so as to be able to keep an imprint of the information we receive. How? The synapses are modified and, as a result, the transfer of the message via the neurotransmitters is more effective. This is what is called synaptic plasticity. It is thought that the β A fragment obstructs this elegant mechanism. A recent study has indeed revealed that the fragment diminishes the number of glutamate type receptors on the neurons' surface, thus impairing the quality of transmission.

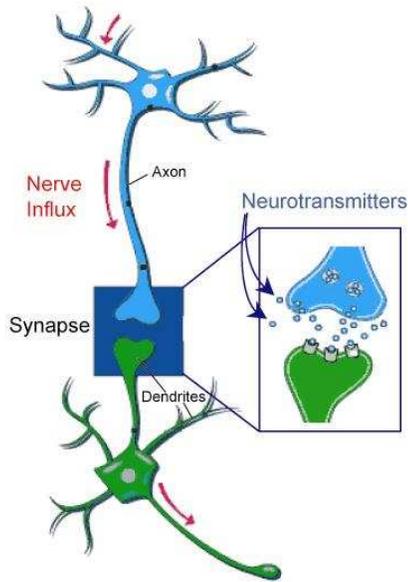


Fig.3 Structure of a synapse. The nerve impulse is conveyed from one neuron to another thanks to the release of neurotransmitters in the synaptic cleft.

The withering away of the glutamate and acetylcholine neurons justifies the use of certain drugs, of which the most current are Exelon, Aricept and Reminil. Their object is to limit the degradation of acetylcholine in the synaptic cleft and so increase its lasting effect. In so doing, they compensate the cholinergic deficiency and improve memory performance. Yet another drug, known as Memantine, acts on a certain type of glutamatergic receptor. In AD, these receptors can initiate a cascade of toxic intracellular reactions, probably due to the βA fragment. By temporarily blocking these receptors, Memantine protects the neurons, and so reduces cognitive disorders. This appears to contradict what has just been said, i.e. that fewer receptors affect neuron transmission. Yet the beneficial effects are there to be seen and the apparent contradiction just goes to show how complex cellular interactions are. Be that as it may, both therapies are symptomatic treatments that are far from perfect and whose effects are modest. Since it is so difficult to give an early diagnosis of AD, drugs are only prescribed at a relatively advanced stage. Unfortunately, the illness progresses relentlessly on its degenerative course and the drugs offer no hope once the neurons are destroyed.

The egg or the chicken

Neuronal dilapidation progresses from neuron to neuron. As far as ND is concerned, lesions have been shown to follow a defined course. They are triggered off in the most vulnerable regions of

the brain, the entorhinal cortex and the hippocampus, where new memories are stored. As mentioned above, the first symptoms of cognitive disorder are memory problems. Progressively, the lesions spread to the whole of the cortex: they overrun the isocortex - the center where sensory information is gathered - then reach the reception areas of our five senses and the motor area where orders are elaborated. With regard to the senile plaques, they appear first in the isocortex and are then associated with the ND.

It has long been thought that the senile plaques are the first lesions to appear. This theory known as the "amyloid cascade" holds that the accumulation of βA fragments results in ND degeneration and ultimately neuron death. Such a hypothesis is supported by family cases of AD where mutations in the amyloid protein or the presenilins lead to an overproduction of βA . Moreover, the gene of the amyloid/ βA protein is located on chromosome 21, which would explain why a person with Down's syndrome has three copies of the gene. It is a fact that on approaching the age of 40, all patients with Down's syndrome develop AD. This observation reinforces the "amyloid cascade" theory.

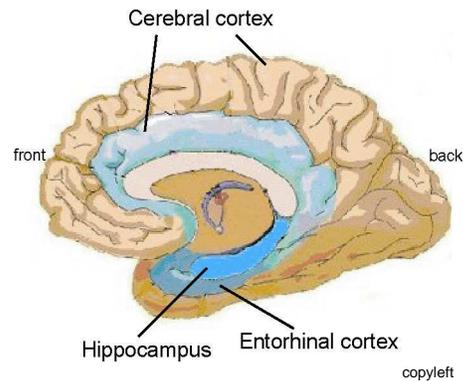


Fig.4 The cerebral regions affected by the lesions. Neurofibrillar degeneration proceeds from the hippocampus to the cerebral cortex via the entorhinal cortex; the senile plaques affect the whole of the cerebral cortex.

Nonetheless, senile plaques are not confined to AD alone. Indeed, they are present in the normal ageing process of the brain but in smaller quantities - proof that the organism can tolerate amyloid deposits up to a certain degree, though to which degree exactly is difficult to define. Currently, there is strong disagreement on the subject of the "amyloid cascade", for two reasons in particular. Many investigations have underlined the fact that, in most cases, ND occurs before any senile plaques appear. Moreover, the seriousness of clinical symptoms is measured according to the evolution of ND: the sole appearance of senile plaques is not a reliable guide.

And which is first to strike? Amyloid β protein? Or protein tau? There are various conflicting theories. However, all strive to propose a scenario that reunites both the formation of senile plaques and ND. Which comes first? And what influence does the one have on the other? Do they progress together? Is there a common denominator? From what molecular process do these two lesions originate? So many questions for one problem alone: the causes of this disease are still well hidden.

Avoiding the disease

Genes whose mutations lead to early forms of AD have been discovered. Could that imply that there are risk factors? Without doubt, age is the most important. Moreover, factors of genetic predisposition have been identified, such as the apolipoprotein E (ApoE) gene, for instance. ApoE is well known for its role as a carrier of cholesterol in the bloodstream. In humans, there are three types of ApoE². Although not a determining factor, ApoE4 considerably increases the chances of the illness developing. 30% to 60% of AD patients are estimated to be carriers. How does ApoE4 act? It could be one of the causes of the amyloid deposits, thus contributing to the growth of the senile plaques.

Environmental factors such as hypertension, smoking, hypercholesterolemia, a diet low in antioxidants or a severe head injury can also bring about AD. Several studies also suggest that a poor level of education in childhood could be a contributing factor. As for estrogens, they seem to have a beneficial effect on the brain; consequently, menopause could be a risk factor and women may well be more predisposed to AD than men.

Towards a cure?

Alzheimer's disease is very difficult to diagnose, for three reasons in particular. First, the initial signs of AD coincide exactly with those of the

² A gene can exist in a number of different forms. As a consequence, so can proteins. And such an event is known as polymorphism. Proteins are made up of a chain of molecules – or amino acids – selected from a choice of 20 amino acids. A protein's sequence determines the structure and function of the protein, in the same way as a sequence of notes in a music score determines a tune.

However, even though we all sport the same kind of proteins, which ensure the same kind of functions, there are details which vary from one person to another. For instance, a protein can have the same function though it may differ by one amino acid in two different people. Much in the way that a varying note in a symphony is not a false note but just the composer's fantasy. Such a note is called a polymorphism in biology. cf. "In vino veritas"

normal ageing process. Second, the cerebral lesions are microscopic and can only really be detected via an autopsy. Third, no biological molecule can be reliably detected in the bloodstream or in the cerebrospinal fluid, i.e. the fluid around the brain tissues and the spinal cord.

What should one do when one's memory fails persistently and AD becomes a haunting possibility? It is in fact relations who fear the oncoming of the disease, since those directly concerned usually underestimate their cognitive deficiencies. Frequently, they are advised to have "memory consultations", where they are subjected to a whole gamut of neuropsychological tests that are supposed to determine the extent of their cognitive disorders. In an effort to fine-tune the diagnosis, MRI (Magnetic Resonance Imaging) analyses may be resorted to, where MRI reveals atrophied areas of the brain in the hippocampus, for instance. A brain SPECT (Single Photon Emission Computed Tomography) can also be performed on a patient and is a way of measuring the cerebral blood flow which testifies to the brain's activity. Such techniques have raised great hopes in giving an early diagnosis of AD.

It is common practice to prescribe Memantine and drugs that inhibit the deterioration of acetylcholine, though they only serve to delay temporarily the degeneration of neurons. Currently, many believe that vaccination might be the answer. Why? The purpose of vaccines is to stimulate the production of antibodies against specific proteins and, in order to do so, all you need to do is inject the said proteins into the organism. The idea would be to "clear away" the senile plaques by stimulating the production of antibodies against the β A fragments. There have been tentative clinical trials but they have had to be discontinued due to some cases of encephalitis. But in 2006 and on their own initiative, Roche will carry out a new series of trials, in which they will inject anti- β A antibodies directly to AD patients so as to prevent an inflammatory reaction. Furthermore, other clinical trials were initiated with Alzhemed (a drug developed by Neurochem) in Switzerland last autumn, which should act on the senile plaques before they actually appear by directly blocking the aggregation of β A fragments.

There are many therapeutic trails based on various strategies which all aim to check the evolution of AD lesions...and as much hope for patients struck with Alzheimer's disease for a cure that will give them complete recovery of their identity.

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For further information

On the Internet:

- Alzheimer Society of Canada :
<http://www.alzheimer.ca/english/index.php>
- On the memory: "PP1: Tracking down the protein of Forgetfulness" :
http://www.expasy.org/prolune/pdf/prolune009_en.pdf
- Unité INSERM "Vieillessement cérébral et dégénérescence neuronale" in Lille :
http://www.alzheimer-adna.com/Alz_/Alzheimer.sommaire.html

A little more advanced (in French):

- Dossier Pour la Science on the memory and Alzheimer's disease : "La mémoire - Le jardin de la pensée", number 31, avril 2001
- Book : Schenk, Leuba and Büla, "Du vieillissement cérébral à la maladie d'Alzheimer", november 2004, editions De Boeck Université, ISBN : 2-8041-4595-6

Illustrations:

- Heading illustration (Sleep by Salvador Dali), Source:
http://www.lecerveau.mcgill.ca/flash/i/i_07/i_07_p/i_07_p_oub/i_07_p_oub.htm
- Fig.1, Source: <http://en.wikipedia.org/wiki/Image:Alzheimer01.jpg>
- Fig.3, Adaptation :
http://www.droques.gouv.fr/fr/savoir_plus/livrets/action_droques/action_page2.html
- Fig.4, Adaptation :
http://www.lecerveau.mcgill.ca/flash/a/a_07/a_07_cr/a_07_cr_tra/a_07_cr_tra.htm

At UniProtKB/Swiss-Prot:

- Amyloid beta A4 protein [Precursor], Homo sapiens (human): P05067
- Presenilin-1, Homo sapiens (human): P49768
- Microtubule-associated protein tau, Homo sapiens (human): P10636
- Apolipoprotein E [Precursor], Homo sapiens (human): P02649

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