Facts
Series

Alzheimer

VIB
science meets life

Contents

Summary

Worldwide, 35 million people suffer from Alzheimer's disease. It is the most common cause of dementia. The disease has an insidious onset consisting of vague initial symptoms that can include forgetfulness and difficulty with planning. As the months and years go on, however, the indications become clear. People with Alzheimer's disease become disoriented in time and space, the gaps in their memory become more obvious, they have difficulties with routine tasks such as cooking, washing, dressing and shopping. They become increasingly dependent on others. They often need to be admitted to a nursing home.

The main risk factor for Alzheimer's disease is old age - as soon someone is over 65, the risk of Alzheimer's disease doubles every five years. To illustrate: fewer than 1% of people between 60 and 65 have the disease, but this rises to 30% for people over 90. Despite this, it does sometimes occur in people under the age of 65. This is called 'early-onset Alzheimer's'.

In the brains of people with Alzheimer's, the nerve cells die at an accelerating rate. A great deal of research has been done into this degeneration of brain cells, some of it by VIB scientists. The clumping-together of toxic protein fragments in and next to the brain cells is the first stage in the long-term progression of the disease. Initially, the brain tries to compensate for the damage but, in the end, it loses the fight. The result is that the connections between the nerve cells become increasingly damaged and the nerve cells die off. As a result, cognitive functions such as memory, attention, concentration, perception, thinking and language become impaired and patients can show subtle behavioral and personality changes.

This background file provides an overview of the latest scientific insights into Alzheimer's disease. Naturally, only an outline of these can be given here. This is because over the past 20 years alone some 80,000 articles have been published about this disease (in comparison, 130,000 scientific articles about AIDS have been published over the same period and more than 3 million about cancer). But even 80,000 Alzheimer's articles are impossible to summarize in one document. Moreover, the research is gathering momentum. For example, we have learned more about Alzheimer's disease in the last two decades alone than in the 100 years before.

Despite this, there is still no cure. The search for a solution is difficult. Researchers, doctors and pharmaceutical companies have made enormous efforts in recent decades to find new drugs against the disease. No medicine has been found that can cure Alzheimer's. Yet we must continue, say the researchers, if we are ever to halt the disease.

However, some hopeful news recently appeared in the scientific press: there are indications that the number of patients is levelling-off, despite the ageing population. This effect can be seen especially in Western countries and amongst the better educated. It is possible that a healthy and active lifestyle, a varied social life and abundant cognitive stimulation protect people against dementia and Alzheimer's disease. In short, healthy eating, exercise and staying socially and intellectually active are good for the brain as well as the heart and circulation.

LOTS AND JOOP

their story

The feeling that something's not right

It's not right. It's not right that you forget things ... says Lots. It didn't go well. Just forgetting things you did. Or even things you're doing. All of sudden, they're just gone. All gone. Names, facts, events, etc. you know nothing about them anymore. People say 'Oh no, there's nothing wrong. It happens to me as well. I've always been bad at names. It will soon pass'. But, that doesn't figure ... you feel that something ominous is coming. My mother had Alzheimer's too. It's the first thing you think about.

It must have been 2007 or 2008, says her husband Joop. You try to deny it at first - to minimize it. But the doubt hits you. You lie awake at night. You sink slowly and reluctantly through the denial. The turning point for me was a meeting with a Georgian colleague. He spent an evening with us at home. Including dinner. When I received an invitation to go to Georgia two months later, Lots remembered nothing about that meeting. You might forget a brief conversation with a stranger - but a whole evening ... ?

Lots must have been 68 then. That's young for Alzheimer's. But we got increasingly concerned about it. Our youngest daughter noticed that something was wrong. Time to see the doctor, I thought.

Examine
and you
will know everything
but dementia makes
me forget.

If
the result
is senile dementia
what must I then
know?

Lots Stam-Vermeulen

A wandering memory

An insidious process

Alzheimer's disease is the leading cause of dementia.[1,2,3,4,5] It is a chronic condition that affects the brain. Slowly at first, but more and more severely as time goes on. Initially, people with the condition have trouble storing new information and experiences. It seems that recent events are quickly 'forgotten'. Loss of short-term memory. Gradually, however, other memory-related and cognitive functions are affected. There are problems with thinking and language, orientation, mood, motivation and self-care. Some patients also exhibit behavioral problems.

The changes increase. Eventually, the patient becomes totally dependent on others. At this stage, many people with Alzheimer's disease are admitted to a nursing home. The loss of memory can be dramatic - patients no longer recognize their own spouse, children or grandchildren. They also start to decline physically: they lose weight, become bedridden, have difficulty chewing and swallowing, etc. On average, people with Alzheimer's live for eight to ten years after the diagnosis. However, this varies from person to person - some patients die after only three years, others after twenty. Although the condition mainly affects people over 65, there is also a form that occurs at a younger age. About 5 to 10% of the patients are diagnosed with Alzheimer's before they reach 65.

NOT EVERY FORM OF DEMENTIA IS ALZHEIMER'S

In addition to Alzheimer's disease, there are about 60 other causes of dementia. Between 50% and 70% of all patients with dementia suffer from Alzheimer's disease. Other common forms are vascular dementia, fronto-temporal dementia and Lewy body dementia, each making up about 10-15% of the total.[a]

***Vascular dementia** is characterized by the occurrence of strokes (cerebral infarctions or CVAs). This is also called multi-infarct dementia. A cerebral infarct happens when a blood clot or hemorrhage disturbs the flow of blood in the brain. The surrounding brain cells do not get enough oxygen and die, which results in loss of function. It occurs in 10 to 15% of people with dementia. For a further 10 to 15% the cause is a combination of vascular dementia and Alzheimer's.*

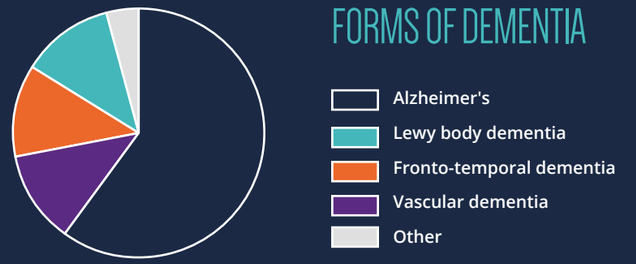
***Fronto-temporal dementia** is a group of dementia clinical pictures in which the damage occurs mainly in the frontal and temporal lobes of the brain. In contrast to Alzheimer's disease, memory loss is not the first symptom to appear in patients with fronto-temporal dementia. Instead, it is characterized more by language disorders and/or behavioral and personality changes. Some people with fronto-temporal dementia seem apathetic and exhibit a lack of initiative. In other people disinhibition gets the upper hand: spending money lavishly, making grand but unrealistic plans, disinhibited eating, loss of ethics, etc.*

***Dementia with Lewy bodies** results from the accumulation of a number of abnormal proteins, called Lewy bodies, in brain cells. The symptoms are dementia, fluctuations in attention and concentration and visual hallucinations. In addition, sluggish movement and tremor (shaking) may occur (Parkinsonism).*

Other less common causes of dementia include Huntington's disease, multiple sclerosis, AIDS, Creutzfeldt-Jacob disease, Parkinson's disease and excessive alcohol consumption.

The 'standard' classification given above, however, is under pressure as a result of new insights from molecular and genetic research. At the molecular level, there is a strong overlap between various forms of dementia, with the result that more and more researchers are speaking about a 'continuum' of diseases that includes Parkinson's disease and amyotrophic lateral sclerosis (ALS).[b, c, d]

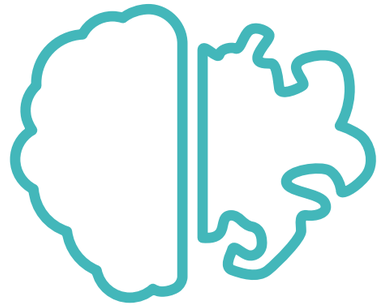
FORMS OF DEMENTIA



Neurodegeneration

What is immediately apparent about the brains of deceased Alzheimer's patients is the size and shape of those brains. The massive death of nerve cells causes them to be smaller, with large indentations and even holes. This loss of brain cells is most striking in areas that play a role in memory (including the hippocampus) and at thought processes (such as the cerebral cortex).

HEALTHY BRAIN



ALZHEIMER'S BRAIN

At the start of the 20th Century, the German neurologist Aloïs Alzheimer, after whom the disease was named, discovered a number of additional characteristic features in the brains of his patients.[6] At the time, these features were only visible under the microscope:

- **amyloid plaques *between* the nerve cells**
  these plaques consist of an accumulation of the remains of brain cells and what is called βeta-amyloid (Aβ). These protein fragments come from the degradation of the larger amyloid precursor protein (APP - See also the box 'Plaques with ß-amyloid protein fragments', on page 9).
- **neurofibrillary tangles *inside* the nerve cells**
  these are insoluble, intertwined protein fibres that accumulate in nerve cells. They consist of Tau protein that is 'hyperventilated' (see also the box 'Tau tangles' on page 17).

A historical revolution in research

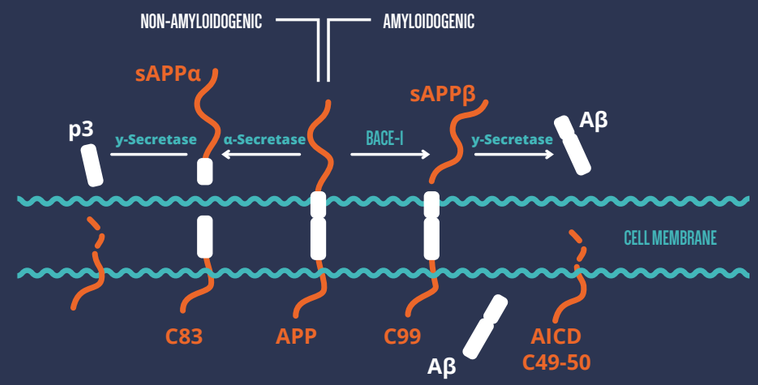
Aloïs Alzheimer saw the plaques and neurofibrillary tangles under his microscope but did not know what caused them. It would be the 1980s before the Aß and Tau proteins were identified as major components of, respectively, the plaques and the neurofibrillary tangles.

This discovery immediately led to a huge breakthrough in Alzheimer and dementia research. The idea that a biochemical process was the cause of a complex cognitive disorder like Alzheimer's disease turned Alzheimer research upside down. Earlier descriptive accounts had led researchers to focus on molecular and cellular research to explain the causes and disease mechanisms and to devise clinical interventions. That led to dozens of diagnostic and therapeutic clinical trials for an illness which had been previously thought to be either incurable or an inevitable consequence of ageing.

We now know that the accumulation of these toxic proteins and protein fragments in the brain leads to stress and damage: the energy metabolism of the nerve cells is disrupted and the connections between nerve cells (synapses) are damaged. The immune system tries to repair this, but eventually and inevitably fails and the nerve cells die *en masse*.

PLAQUES WITH β-AMYLOID PROTEIN FRAGMENTS

One of the most important microscopically visible features in the brains of Alzheimer's patients are the amyloid plaques. They are formed by an agglomeration and precipitation of what are known as β-amyloid fragments (Aβ), which are degradation products of amyloid precursor protein (APP). APP is a protein found in the cell membranes of brain cells. New APP molecules are constantly being created and the old ones broken down and removed.[a b]



As shown in the illustration, APP can be broken down in either of two ways: a harmless, non-amyloidogenic way (left) and a less harmless way (right) that generates Aβ-fragments. In the non-amyloidogenic process, APP is sequentially cleaved by the protein complexes α-secretase and γ-secretase to form the protein fragments C83, sAPPα and p3. These fragments are not toxic to the brain cells because they are further broken down or removed.

If, however, APP is cleaved by BACE1 (also known as β-secretase) and then γ-secretase, this creates Aß-fragments with a length between 36 and 48 building blocks (amino acids). These Aß-fragments have a tendency to aggregate (clump together), initially in groups of two to six fragments (oligomers) and eventually become the insoluble, 'plate'-like structures that form the amyloid plaques. The longer forms of Aß, from Aβ42 upwards, are particularly harmful to nerve cells:

- *They impede the functioning of various vital receptor systems in the nerve cells, which then weakens the functional connections (synapses) between neurons.*
- *They are toxic to the mitochondria in the nerve cell. Mitochondria are the 'energy factories' of the cell. Aß undermines the functions of various mitochondrial proteins (including cytochrome c) needed for the nerve to take up oxygen, as a result of which the mitochondrion produces less energy. What's more, non-functional mitochondria produce radicals such as peroxides and reactive nitrogen compounds. These are hyper-reactive molecules that overstress the nerve cells and put them under pressure.*
- *They also attract immune cells from the immune system. Some of these immune cells, however, also release signaling substances (such as interleukin-1, interleukin-6 and tumor necrosis factor α) that provoke inflammatory reactions. These reactions can be detrimental to the surrounding nerve tissue.*
- *Aß deposits also lodge themselves in the blood vessels of the brain. This weakens and narrows the blood vessel wall, the blood flow is disrupted and mini-infarcts can occur.*

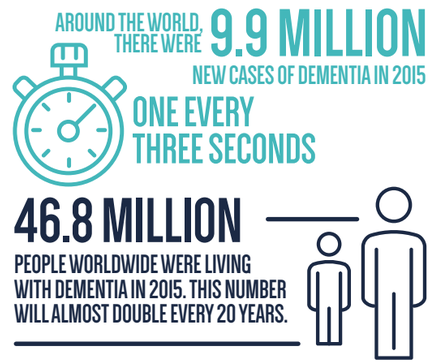
2 Social impact

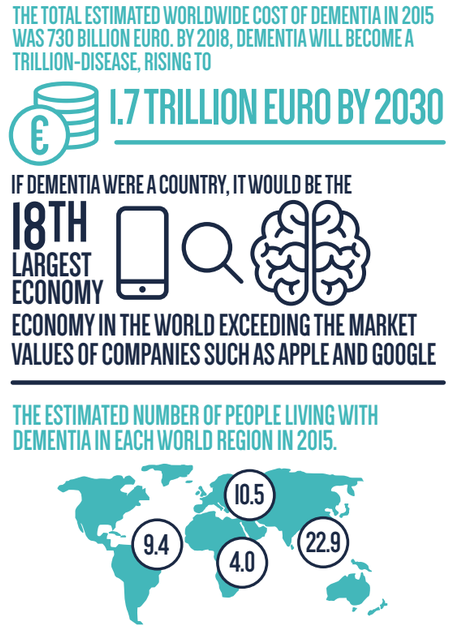
The impact of dementia on the quality of life of the patient and their social environment (partner, family and friends) is enormous. The disease is also a burden on the health system and on society in general.

In numbers

Every three seconds, somewhere in the world someone is diagnosed with dementia, according to Alzheimer's Disease International in its 2015 report on the prevention and social impact of dementia.[7] That means 9.9 million new cases of dementia. And that's every year.

In 2015 there were 46.8 million people worldwide with some form of dementia. That number will increase dramatically in the coming years, again according to estimates by Alzheimer's Disease International. To 74.7 million in 2030 and 131.5 million in 2050, to be precise. The increase is especially noticeable in countries with a low or low-middle income: today 58% of people with dementia live in these countries and in 2050 it will be 68%.





High cost

In 2015 we spent about 730 billion Euro on dementia worldwide, or 35.4% more than in 2010. Just for comparison: in 2014, Belgium's gross domestic product (which is the value of all the goods and services we produce) was 402 billion Euro. The global cost of dementia is therefore almost double the Belgian GDP. To put it somewhat differently, if dementia were a country, it would have the 18th largest economy in the world.

How it used to be...

Lots Vermeulen and Joop Stam met at the fun-fair in Hoorn, just under fifty kilometers north of Amsterdam. Even today, Lots can remember the details of this meeting. It was love at first sight - on condition that Joop was Catholic. A requirement of my mother. We danced on the first night. The next day we saw each other again. That wasn't easy, because Joop was from Hoorn and I was from Purmerend. Nearly twenty kilometers apart. That was a long way in those days. What's more, I was already 22 and Joop was only 20. Was that allowed?

Joop studied medicine in Amsterdam. As a young GP he took part in setting up the first health center in Amsterdam. That would be like a Belgian 'Peoples' Medical Center', says Joop - rather left wing, you know. In addition, he taught general practice at the University of Amsterdam.

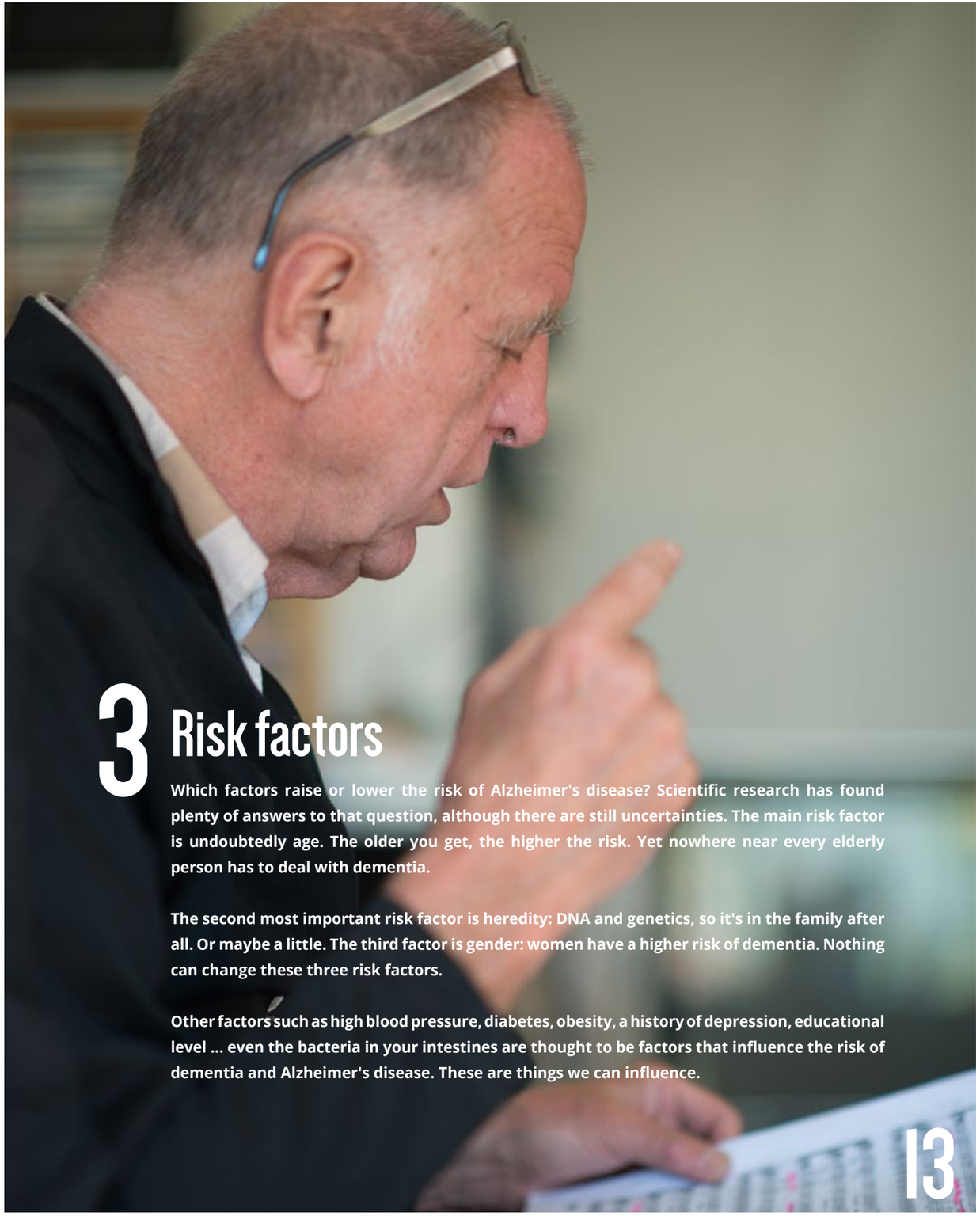
Lots accompanied Joop to Amsterdam. She went to work as an X-ray Laboratory Technician in Amsterdam, and later in Utrecht and Amersfoort. Until the first of their three children started school. Lots retrained herself in crafts. To be at home more. Later she worked as a movement expression therapist. Working with disabled children. Lots relates all this herself, with a bit of help from Joop.

But talking about the start of her illness is harder. That's already well in the past, she says. There are fragments of memory. Fragments that get mixed up. Especially in time.

Joop found this early phase a very difficult time. Do you talk about it to each other or not? Share your concerns or not ... do you dare to be open about it? Are you protecting the other by not talking about it? Or are you hurting each other even more? I never wanted to hide it, added Lots, you'd go mad. I spoke about it straight away.

You lot just carry on, said Lots. Are you angry, I asked?
Lots was angry and sad. She fought back her tears. We - that is, Lots, our two daughters and myself - stood in front of her wardrobes, which weren't tidy any longer. She couldn't find her underwear easily. Me neither. A new phase had started; it got harder for her to take care of herself. And she could no longer sort and order the clothes either. She had lost HER private domain. The dependence increases. And that's hard to take.

Joop Stam



3 Risk factors

Which factors raise or lower the risk of Alzheimer's disease? Scientific research has found plenty of answers to that question, although there are still uncertainties. The main risk factor is undoubtedly age. The older you get, the higher the risk. Yet nowhere near every elderly person has to deal with dementia.

The second most important risk factor is heredity: DNA and genetics, so it's in the family after all. Or maybe a little. The third factor is gender: women have a higher risk of dementia. Nothing can change these three risk factors.

Other factors such as high blood pressure, diabetes, obesity, a history of depression, educational level ... even the bacteria in your intestines are thought to be factors that influence the risk of dementia and Alzheimer's disease. These are things we can influence.

Genetics

There are several indications that heredity plays a role in Alzheimer's disease:

- Half of the patients have at least one other family member with the condition.
- In addition, twin studies have revealed a genetic component - if one identical twin develops Alzheimer's disease, the other has an 80% chance of developing it as well.

With hereditary, however, a clear distinction needs to be made between early-onset and late-onset Alzheimer's. The genetic contribution to early-onset Alzheimer's is much greater than in the more usual form of the disease, which occurs in old age (after 65 years).

Early-onset Alzheimer's

Most of the patients who develop early-onset Alzheimer's are diagnosed between 45 and 65 years of age. But it can also occur earlier. In a number of Belgian families with early-onset Alzheimer's, the average starting age of onset is 35 ± 6 years. The youngest patient even showed all symptoms at 21 years and died at 28.

About 10% of the patients with Alzheimer's disease have the early-onset form of the condition. In this group, 10% have clearly inherited the condition according to the autosomal dominant pattern.[8] This means that these peoples' Alzheimer's disease is caused by an abnormal gene. If they pass on this abnormal gene to their children (each of whom has a 50% chance of inheriting the abnormal gene), the children will have a greatly increased risk of developing early-onset Alzheimer's disease.

This often involves mutations (heritable errors) in the genes that code for the APP-, PSEN1- or PSEN2 proteins that form part of γ-secretase (see box 'Plaques with β-amyloid protein fragments'):[9]

- Mutations in APP were found by molecular genetic studies of large families in which early-onset Alzheimer's is passed on from one generation to the next. These mutations also affect the production of Aß-amyloid.
- The PSEN1- and PSEN2-proteins play a role in the breakdown of APP. The mutations in these genes ensure that breakdown of APP is altered such that it generates more long and toxic Aß than normal (see box 'Genetics supports the amyloid hypothesis').

Mutations in APP, PSEN1 and PSEN2 only account for a small fraction of patients with an obviously heritable form of early-onset Alzheimer's disease. But the search goes on for other genes.

Late-onset Alzheimer's

The first genetic risk factor for the more common form of Alzheimer's disease - the type that occurs after the age of 65 - was found by molecular genetic studies in families in which there were multiple patients but no clear pattern of inheritance. It turned out to involve the ε4-variant of the gene that codes for apolipoprotein E (APOE). The APOE gene occurs in various forms throug-out the population. APOE ε2, APOE ε3 and APOE ε4. We all carry two copies of the APOE gene in our DNA - one from our mother and one from our father.

If you have one copy of the APOE-ε4, you have three times the risk of developing Alzheimer's disease; if you have two copies, you have 15 times the risk. APOE is undoubtedly the most important risk gene for Alzheimer's disease and accounts for up to 20% of late-onset Alzheimer's disease.[10] More recently, other risk genes were found, each of which makes a small contribution to the total genetic risk for Alzheimer's disease. The most important of these are TREM2, CLU, CR1, PICALM and BIN1.[11, 12, 13, 14, 15]

None of these genes can cause the disease by itself. Consequently, the various risk genes are combined into a risk profile that classifies patients according to the risk they face. This has advantages for scientific research, clinical trials and, later, for the development and prescription of personalized medication, treatment and even prevention.

GENETICS SUPPORTS THE AMYLOID HYPOTHESIS

The production of toxic Aß variants and the inability of the brain cells to remove them was seen, from the mid-1980s onwards, to be the main cause of Alzheimer's disease. This 'amyloid hypothesis' claimed that the deposition of Aß leads to progressive damage to the connections between the nerve cells, inflammatory reactions, death of nerve cells and, ultimately, dementia.[a b] An important argument in support of the amyloid hypothesis came from the genetic forms of the disease:

- *PSEN1 (presenilin-1) and PSEN2 (presenilin-2) are proteins that form part of the y-secretase protein complex that cuts APP (see box 'Plaques with β-amyloid protein fragments'). As a result of the mutations in APP or one of the PSEN genes, the breakdown of APP shifts more in the direction of production of the toxic longer Aß fragments. [c]*
- *People with a duplication of the APP gene also have an increased risk of Alzheimer's disease. [d, e] The same is true for people with Down's syndrome. They have 3 copies of chromosome 21 instead of 2. This is the chromosome with the gene for APP. Consequently they also have three copies of the APP gene, which makes them more predisposed to Alzheimer's disease. [f]*
- *However, things can also go in the other direction. There are genetic variations in APP that cause the splitting BACE1 complex to produce far fewer toxic Aß fragments. This genetic error protects against Alzheimer's disease. [g, h]*
- *In dozens of animal models in which the above mutations were introduced, cognitive symptoms appeared that resemble dementia in humans. [i]*

Age and gender

Age is undoubtedly the most important risk factor for many forms of dementia, including Alzheimer's disease of course. We can assume that in Western Europe 2% to 3% of the 65- to 69-year olds show symptoms of dementia. That figure increases rapidly with age: for individuals between 85 to 89 years it is 20.5%, and rises to 39.8% for people over 90. An estimated 50% to 70% of these patients have dementia of the Alzheimer type.[16]

It is also noticeable that the incidence of dementia (and Alzheimer's disease) is higher for women than men across all age groups.[17, 18] There is no clear biological explanation for this. Some researchers believe that women are more sensitive to the pathological lesions that form in the brain. Others attribute it to the effects of post-menopausal hormonal changes.

Global burden of disease	Number of included studies		Gender	Age group						
	Number in age-specific meta-analysis	Number in age- and gender-specific meta-analysis		60-64	65-69	70-74	75-79	80-84	85-89	90+
Western Europe	65	54	M	1.1	1.8	2.8	4.7	7.8	12.6	23.7
			F	2.0	3.2	5.2	8.7	14.6	23.7	45.1
			M and F	1.6	2.6	4.3	7.3	12.4	20.5	39.8

Lifestyle and other factors

In addition to age and genetics there are various environmental factors associated with Alzheimer's disease. The factors that show up in multiple epidemiological studies are:[19, 20]

- cardiovascular risk factors:
  - high blood pressure in middle age
  - diabetes
  - obesity in middle age
- psychosocial factors:
  - a history of depression
  - educational level: high-skilled people seem to be better protected against Alzheimer's disease
- lifestyle factors:
  - smoking
  - low physical activity
  - low cognitive activity

Traumatic brain injury (e.g. a hard blow to the head) can lead to Alzheimer's disease decades later.[21] Too many blows to the head in boxing or American football would also be a factor in the disease, and giving too many headers in soccer would have a similar effect. In addition, a poor sleep pattern could play a role, as could some nutrients.[22, 23] Unlike the above-mentioned environmental factors, however, these connections need to be confirmed by further scientific research.[24]

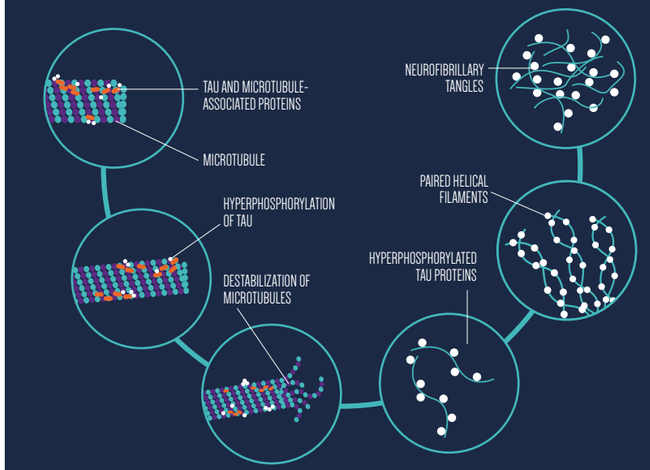
An environmental factor that has recently been linked to Alzheimer's disease is the intestinal flora - the micro-organisms in the digestive tract. Recent studies have shown that some intestinal bacteria affect the development of neurodegenerative diseases, including Alzheimer's.[25, 26, 27] These results also need to be confirmed.

We should note that none of the risk factors (other than age and heredity) have been irrefutably linked to the disease. For example, there is no single factor with a link to the disease that is as strong as that between smoking and lung cancer. As a result, there can be no scientifically-based advice about the best way to protect against Alzheimer's disease. Nevertheless, we can, as will be shown later in this background file, perhaps reduce the risk by a combination of healthy lifestyle factors. Lifestyle is therefore a potential target for preventive steps that could limit the further increase in the number of dementia sufferers.

TAU TANGLES

When they examined the brains of Alzheimer's patients under the microscope, doctors found, in addition to amyloid plaques, neurofibrillary 'tangles'. These are inclusions of insoluble protein tangles in the nerve cells. The main component of the tangles is the Tau protein in a 'hyperphosphorylated' form. [a]

Tau is an important component of the microtubules. These are tubular structures that form the 'cytoskeleton', which is the skeleton of the cell. In addition to forming the supporting structure of the nerve cell, microtubules are also important for transporting (bio) molecules within it. They form, so to speak, the streets and highways along which biomolecules are transported.



If Tau bears a 'normal' number of phosphate groups (-PO4), it promotes the construction and stability of the microtubules. If there are too many phosphate groups on Tau, however, it detaches from the microtubles, causing them to separate and break up. Moreover, the Tau molecules released by this breakup then stick together into 'paired helical filaments'. These are toxic to the cell. The filaments condense further to form insoluble fibres (tangles). [b]

Unlike mutations in APP, however, changes in the Tau gene do not lead to Alzheimer's disease but to some other forms of dementia, especially hereditary fronto-temporal dementia. Over 30 such mutations have been found in Tau. Neurofibrillary Tau inclusions are, moreover, not specific to Alzheimer's disease. They also occur in other neurodegenerative disorders that may or may not be associated with dementia.

4 Research leads to new insights

Alzheimer

From the biochemical phase ...

Recent research suggests that the abnormal deposits of Aß and hyperphosphorylated Tau in the brain only represent the first phase of Alzheimer's disease. Even if the accumulation of these proteins in and next to the nerve cells leads to additional cellular stress, there must be other decisive factors present to put the brain on the road to dementia. Researchers believe that to understand the complete mechanism behind Alzheimer's disease, they need to see the known Aβ- and Tau-complex cellular biochemistry in the complex cellular context of the brain.

They talk about the 'biochemical phase' of Alzheimer's disease and the subsequent 'cellular' phase. In the second phase, complex feedback and reinforcing mechanisms are at work. We do not yet fully understand these mechanisms, but we do know that different cell types are involved - not just neurons. The interactions between all these cells determine whether the brain remains in balance. Only when this balance is lost do the first signs of dementia occur, and only then do we get into the 'clinical' phase.[28]

... through the cellular phase ...

In recent years, biochemical research on Alzheimer's disease has shifted somewhat towards this cellular phase. Researchers now investigate, amongst other things:

- **How to failing blood vessels in older brains contribute to Alzheimer's disease**. Most Aß fragments are cleared away via the bloodstream. To do this, however, they need to get through the blood-brain barrier. The blood-brain barrier is a shield that separates the circulatory system from the brain cells in order to prevent bacteria, viruses, large or undesirable molecules from entering the brain. We now know that Aß damages that barrier. This makes the blood vessels fragile and they start to leak. Leaking blood vessels lead, in turn, to increased production of Aß. This is, in other words, an example of a self-reinforcing mechanism.

- **The role of nerve cells and their networks in the long-term, complex cellular phase of the disease.** Aß-stress leads to hyperactivation of nerve networks, which evokes a complex pattern of neuronal actions and reactions. Researchers found that abnormalities in these networks are insufficiently compensated by more 'inhibitory' networks. This was particularly the case for neural networks involved in learning and memory.

- **What roles are played by astroglia, microglia and oligodendrocytes?**
  - **Astroglia** are star-shaped support cells in the brains. One astroglial cell can, with its many tentacles, contact some 140,000 synapses (contact points between nerve cells). They thus play an active role in the formation of synapses and synchronize processes in the nerve connections. Prolonged exposure to Aß changes many biochemical pathways in the astroglia. The cells try to compensate for this, but sometimes harmful overcompensation can result.

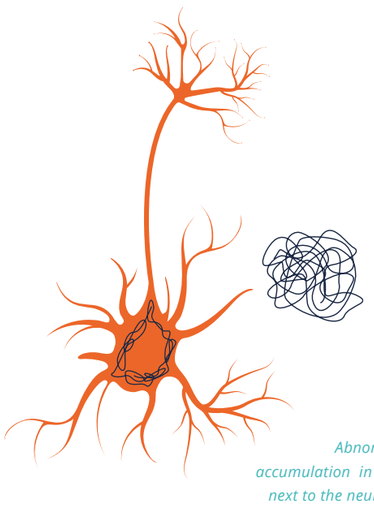
  - **Microglia** are the 'immune cells' of the brain. These mobile cells make up about 5 to 12% of all brain cells. They are constantly looking for foreign substances such as viruses or bacteria. They remove these by literally 'eating' them, a process called phagocytosis. Microglia also play an important role in

BIOCHEMICAL PHASE

- Aggregate stress
- Clearance problems
- Ageing

Abnormal Aβ

- Aβ-oligomer formation
- Aβ-spreading
- Aβ-membrane interactions
- Aβ-oxidative stress



Abnormal accumulation in and next to the neurons

Abnormal Tau

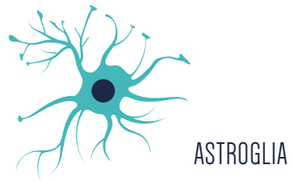
- Hyperphosphorylation
- Tau-oligomers
- Tau-spreading
- Tau-protein interactions
- Tau-mislocalization

CELLULAR PHASE

- Damaged blood vessels
  - Damaged blood brain barrier
  - Increased Aβ production
  - Alteration in APP metabolism
- Disturbance function support cells (astroglia, microglia, oligodendrocytes)

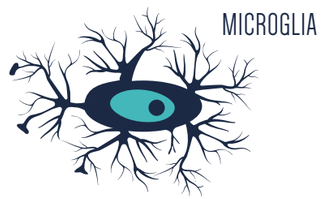
Astroglia

- Disturbance biochemistry astroglia
- Cell death astroglia
- Reduction plasticity neurons



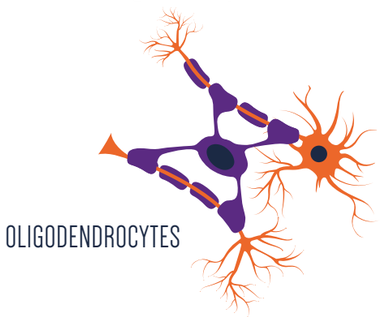
Microglia

- Activation microglia
- Immune response and inflammation



Oligodendrocytes

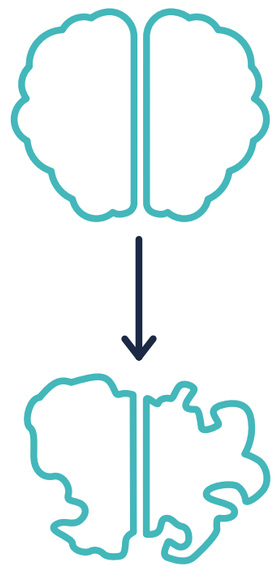
- Myelin breakdown
- Cell death oligodendrocytes



CLINICAL PHASE

Characteristics

- Alterations of proteins in cerebrospinal fluid
- MRI and PET-scan changes
- Hippocampal shrinkage
- Dementia



clearing away Aß deposits. At the same time, they release chemical signals that trigger inflammation. These reactions may be protective under some circumstances, but in other situations they can damage the surrounding tissue. It is also striking that some Alzheimer's risk genes are mainly active in microglia. These include ABCA7, CR1, CD33 and TREM2.

- **Oligodendrocytes** provide an insulating lipid sheath around the branches (axons) of nerve cells. This insulation allows electrochemical impulses to propagate along these nerve branches without creating short-circuits in the brain. Oligodendrocytes are by their nature sensitive to ageing. Even a healthy 'old' brain will have only 70% of its original number of oligodendrocytes. This decline is even more pronounced in people with an APOE ε4 variant (see the 'Risk factors' section).

  The role of oligodendrocytes in Alzheimer's disease has been studied to only a limited extent. Given their important role in maintaining the electric balance in the brain, they can be expected to play an important role in the onset of dementia.

... to dementia

Aß and Tau certainly play a key part in the development of Alzheimer's, but they are far from being the whole story. If we want to bring a halt to the disease we need to look at the cellular phase, which contains tipping points that turn benign and compensable disturbances in the brain into irreversible and progressive neurodegeneration.

In short, there is no straightforward pathological mechanism behind Alzheimer's disease. There is, rather, a complex pattern of interactions on different levels - genes, proteins, cells, cell networks and various brain regions. That is why scientists talk about a 'network' dysfunction.[29]

There can be no doubt that the research of recent decades has led to the continued unravelling of the Alzheimer puzzle. Thirty years ago, researchers had not much more than two pieces of the puzzle: β-amyloid and neurofibrillary tangles. Today they have already put hundreds of pieces in place.

Despite this, the research has its problems as every piece of the puzzle must be placed 'blindly' as it were, without being able to look at the picture on the lid of the box. Every time a new piece is put in place, researchers get a better idea of one part of the puzzle, but it is still unclear to what extent we can see the whole picture. This presents scientists with an immense task.

Quest for a diagnosis

Lots and Joop first went to their GP. He did a small cognitive test - the Mini Mental State Examination, or MMSE. The result - a score of 29 out of 30. Nothing to worry about. There was relief, Joop remembers. But a nagging feeling remained. Because things kept going wrong with Lots. Ultimately, says Joop, in 2011 we went for a full day of testing at the memory clinic at the Free University of Amsterdam. Again, no dementia, according to the doctors. Again relief. Phone everyone to say it's OK.

In 2012, we went back to the university for a new evaluation. The memory problems were still there. Worse even. Lots also scored less well on the tests. Subjective memory impairment, they said. In short, the tests say 'nothing wrong' ... except that the patient and her family experience problems in daily functioning.

Joop, however, refused to give up. Early in 2013 he asked to see the correspondence between the hospital doctors and their GP. In the report of the extensive examination of 2011 he noticed a remarkable sentence: 'If abnormal values are found in the cerebrospinal fluid, you'll hear from us, doctor.' Joop went looking for those test values and came - after much insistence - to a startling conclusion: the Alzheimer's proteins Aß and Tau were already far from their normal values in Lots in 2011. And not just by a small amount. They were really far off. The hospital doctor had written: 'This could indicate Alzheimer's'. That was a real blow!

Only after two years, following new additional revelations, did the cognitive and memory tests confirm that dementia really was present. We are now in 2014. A year earlier, in 2013, there was evidence of mild cognitive impairment, or MCI in medical jargon. You're doing this for years and finally there's a diagnosis, despite serious memory dysfunction and abnormal Alzheimer's proteins, sighs Joop.

Alzheimer
come outside
the heavy news
must come into
the open.

Spinal fluid
my life essence
turns my mind
from wise woman to
a demented one.

Lots Stam-Vermeulen

5 Improved diagnosis

People who develop dementia have often gone a long way before they get a diagnosis. Thanks to world-wide research efforts, doctors can now make the diagnosis much more accurately - and earlier.

Neuropsychological research

When dementia is suspected, the 'gold standard' test is a psychological assessment, either by a specialized care provider or in a specialist center. The assessment consists of a series of neuropsychological tests and questionnaires, and an assessment of daily functioning. The aim is to ascertain the cognitive deficits. This neuropsychological assessment is usually complemented by a blood test, an electroencephalogram, an MRI scan and/or a glucose-PET scan.

A diagnosis of Alzheimer's disease by means of this 'classical' method, however, has its limitations. Even specialist doctors (neurologists, geriatricians, psychiatrists) or specialized centers (memory clinics, geriatric departments in hospitals ...) only get an accuracy of diagnosis slightly higher than 70%. In fact, only a microscopic examination of the brains, after the death of the patient, can show with 100% certainty whether it was indeed Alzheimer's disease.[30]

Protein tests

Recently, specialist centers have supplemented the 'traditional' series of examinations with biochemical tests on cerebrospinal fluid, which is the fluid surrounding the spinal cord. The main biochemical tests used at the moment measure the concentration of Aβ fragments, total Tau protein and hyperphosphorylated Tau in this fluid.

It is taken by lumbar puncture ('spinal tap') using a hypodermic needle which is inserted between the vertebrae of the spine until it reaches the fluid. A few milliliters are then removed. Cerebrospinal fluid is in direct contact with the brain. Pathological processes that occur in the brains can therefore be detected much faster and more accurately in cerebrospinal fluid than in blood or urine. The occurrence of an excess of total Tau and hyperphosphorylated Tau, and a decrease of Aß-fragments in this fluid (because these fragments are deposited in the plaques) may indicate Alzheimer's disease.

The disadvantage of these tests, however, is that the patient has to undergo a lumbar puncture. Although this is a safe and straightforward test, some patients find it unpleasant. Therefore, tests have recently been developed that can be performed on blood. However, their diagnostic value has yet to be validated in large-scale clinical trials. [31, 32, 33]

PET scan with Aβ or Tau imaging tracer

Furthermore, the degree of Aß deposition in a brain can be visualized by using a specialized scanner, called a PET scanner. For this, 'imaging tracers' have been developed that specifically bind to Aß in the brains of patients to make Aß deposits visible under a PET camera.[34]

This Aß-PET examination is expensive (around 1,000 Euro per patient). Not all patients qualify as it is not yet entirely clear which patients really benefit from the examination. For example, it may be especially useful for people who are very forgetful and have orientation problems. It is known that a third of these people will develop Alzheimer's within two years. However, two-thirds do not. With the amyloid PET scan it is possible to get 90% certainty: for people who have absolutely no visible accumulation of Aß under the PET scan it is virtually certain they will not develop Alzheimer's disease within ten to twenty years.[35]

In the meantime, PET imaging tracer dyes have been developed that show the abnormal accumulation of Tau and hyperphosphorylated Tau in the brain.[36, 37, 38, 39] This imaging test will be even further refined and validated, but the expectation is that this Tau test will soon come on the market.

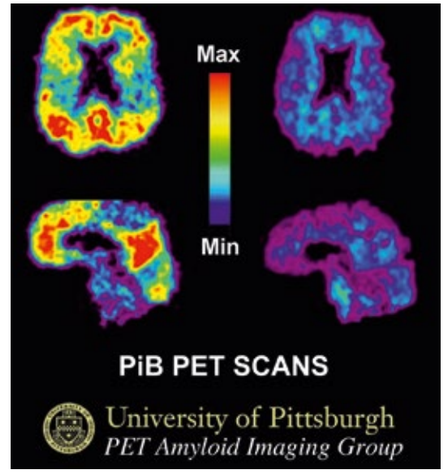
20-year pathology for symptoms

What these biomarkers and PET scans already show is that the initial accumulation of Aß, the hyperphosphorylation of Tau and the formation of neurofibrillary tangles appear 20 years before the first noticeable symptoms of memory loss or other cognitive symptoms. This observation was first made in people with a mutation in PSEN1, which is one of the known Alzheimer's genes.[40, 41, 42] This was later confirmed in patients with the sporadic form of Alzheimer's disease. Specifically, Dutch research indicates that 10% of healthy people in their fifties are already developing an abnormal number of Alzheimer plaques in the brains. Whether these people will develop dementia or memory loss, is still unclear. Future research will tell.[43, 44]

It is in any case already clear that the brain of a patient with Alzheimer's disease will have been a host to a pathological mechanism for more than 20 years before any clinical symptoms appear.

Markers for disease evolution

In addition to detecting the pathology, it is also necessary to establish a clear prognosis. In other words, to get an idea of how fast the patient's condition will deteriorate. To do this, people are looking for markers that show, for example, how much the synapses have been affected. The more seriously the connections between brain cells have been disrupted, the worse the short-term symptoms will be.



PET scan of a patient with Alzheimer's disease (left) and an elderly person without memory disorder (right). The intense red and yellow colors indicate deposition of Aß. (University of Pittsburgh/Wikipedia).

One of these promising new markers is neurogranin, a protein found exclusively in the axons of brain cells. In patients with Alzheimer's disease the levels of neurogranin in the brain and spinal fluid increase, even at early stages of the disorder. Currently, studies with more patients are in progress to further validate these promising markers.[45, 46]

These markers are also important for therapy development (see next section). It is, after all, important for the pharmaceutical companies to be able to select the relevant patients if their tests are to be successful. It is also important to have good markers for monitoring the course of the disease and the effect of the medication. At present there are hardly any markers that give an idea of the severity and progression of the disease. Because the natural progress of the disease is 'slow' patients must be followed over many years to see whether the medication has had an effect. With good 'surrogate markers', the effect would become clear more quickly. This would accelerate the development of new medicines.

LAB ANIMALS IN ALZHEIMER'S RESEARCH

The necessity

The great majority of Alzheimer's research makes no use of lab animals. It involves experiments in test tubes, cell cultures, clinical trials and psychosocial, epidemiological and care-orientated research. Nevertheless, research on animals is inevitable if we want to understand the disease and develop effective treatments.

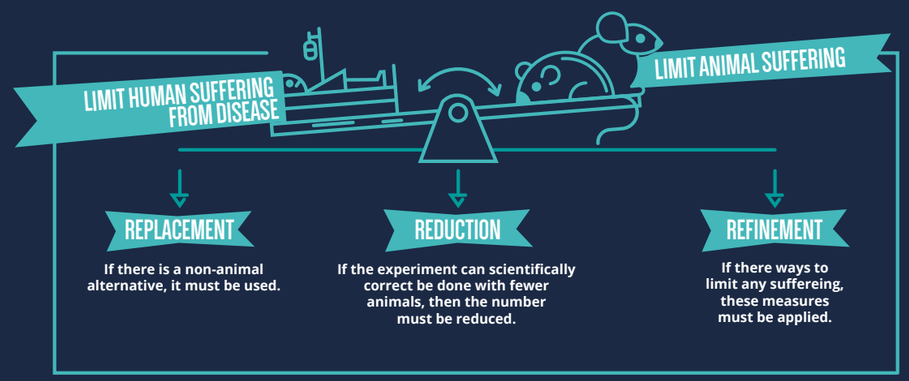
In first instance, research on animals has led to important new insights into the mechanisms behind Alzheimer's disease. Some examples of the mass of data from animal research:

- *Thanks to research on mice, we have been able to study the production of Aß and the aggregation of hyperphosphorylated Tau in living brains and their effects on memory, cognition and behavior. We have been able to find out how certain genetic mutations lead to early-onset Alzheimer's in humans. We can see how the defence mechanism of the brain reacts to toxic protein deposits, how the neural networks get disrupted and why nerve cells die en masse in Alzheimer's disease.*
- *In the brains of fruit flies it was shown that 2 to 4 agglomerated Aß fragments were toxic.*
- *Animal models have confirmed that brain trauma, obesity, mental and physical inactivity contribute to the risk of Alzheimer's disease.*
- *The safety and efficacy of the imaging tracers, which are being used in PET scans to demonstrate amyloid deposition and to allow an early diagnosis of Alzheimer's disease, were first tested in mice and monkeys.*
- *The dozens of drugs that are currently being tested in clinical trials were first extensively evaluated in animal models. Without sufficient evidence that these drugs are safe and potentially effective against the disease, they may not be evaluated in human subjects. Indeed, it is medically and ethically irresponsible to release new, potentially toxic drugs to people without first checking what they do in animal models. Even though that provides no absolute, watertight guarantee that the outcome in people will be as favorable as in the test animals.*
- *There is no other way to reveal the molecular functioning of the brain and brain diseases than research on laboratory animals.*

Careful considerations

All scientists who carry out research on animals do so in a well-considered way. For each new project they weigh the use of animals carefully against its importance to people's health. Moreover, maximizing animal welfare is the top priority:

- *Researchers are only allowed to work with animals if they have undergone sufficient training and education in animal welfare and the ethical use of animals in experiments.[a]*
- *Animal experiments can only be started if they have the approval of the animal ethics committee of the university concerned. In addition, researchers have to make a sound case for why they need animals for the research, give a detailed description of the experiments to be performed, state how many animals will be used (and why so many are needed) and show that the experiments have not already been performed.*
- *Researchers are expected to strictly apply the '3R' principle - replacement, reduction and refinement - of animal experiments. Specifically, they should strive to replace animal experiments as far as possible by test-tube experiments, cell culture and computer models. Furthermore, they should limit the number of animals to a strict minimum and perform experiments in such a way that animal suffering is minimized and animal welfare is ensured. The animals chosen should be those with as low a level of consciousness as possible: if an experiment gives the same results in fruit flies as in mice or rats, the researchers should always choose to carry out the experiment on fruit flies.*



It is simply the case that there are important medical and scientific questions that clinicians and researchers can only answer through research on live animals, as this is needed to take into account all the complex interactions between cells, tissues and organs. It cannot be emphasized enough that research with animals is now one of the most strictly regulated research activities. People often think that this is about research on monkeys, cats and dogs, but the most commonly used laboratory animals are mice, fruit flies and zebra fish, which are bred specifically for research. The animals are housed in the best conditions. Their well-being is even individually registered (for e.g. mice) and observed. Naturally, this leads to significant additional expenditure for the laboratories. This is one more reason why researchers are as sparing as possible in their use of animals and only use animals where there really are no alternatives.

Well-considered animal research also has its place in the search for solutions for Alzheimer's disease. An idea which is, incidentally, also shared by leading patient organizations and organizations that support Alzheimer's research. [c d e]

Preferably no medication

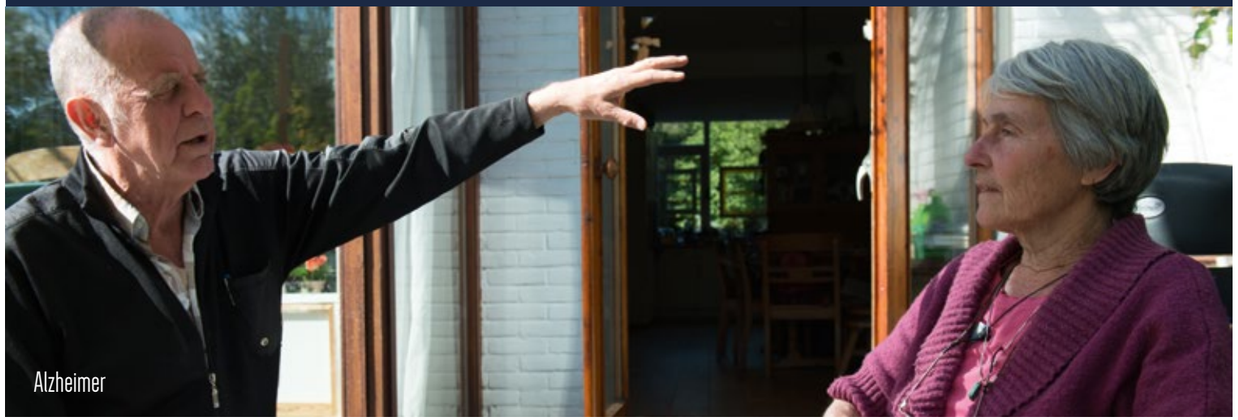
Lots has never taken drugs for her Alzheimer's. I'm not a pill swallower, she says. Never have been. Joop, who had looked up the medical literature, nods: the current medication is a bit trial-and-error, he admits. I estimate that less than half of the Alzheimer's patients in the Netherlands take medicines.

When asked how things are going with her, Lots says with a shrug: 'Pretty good. I find I can still do what I did before.' Though she admits that adjustments are sometimes needed. The frown on Joop's face, however, shows that their lives are being increasingly affected by Lot's condition.

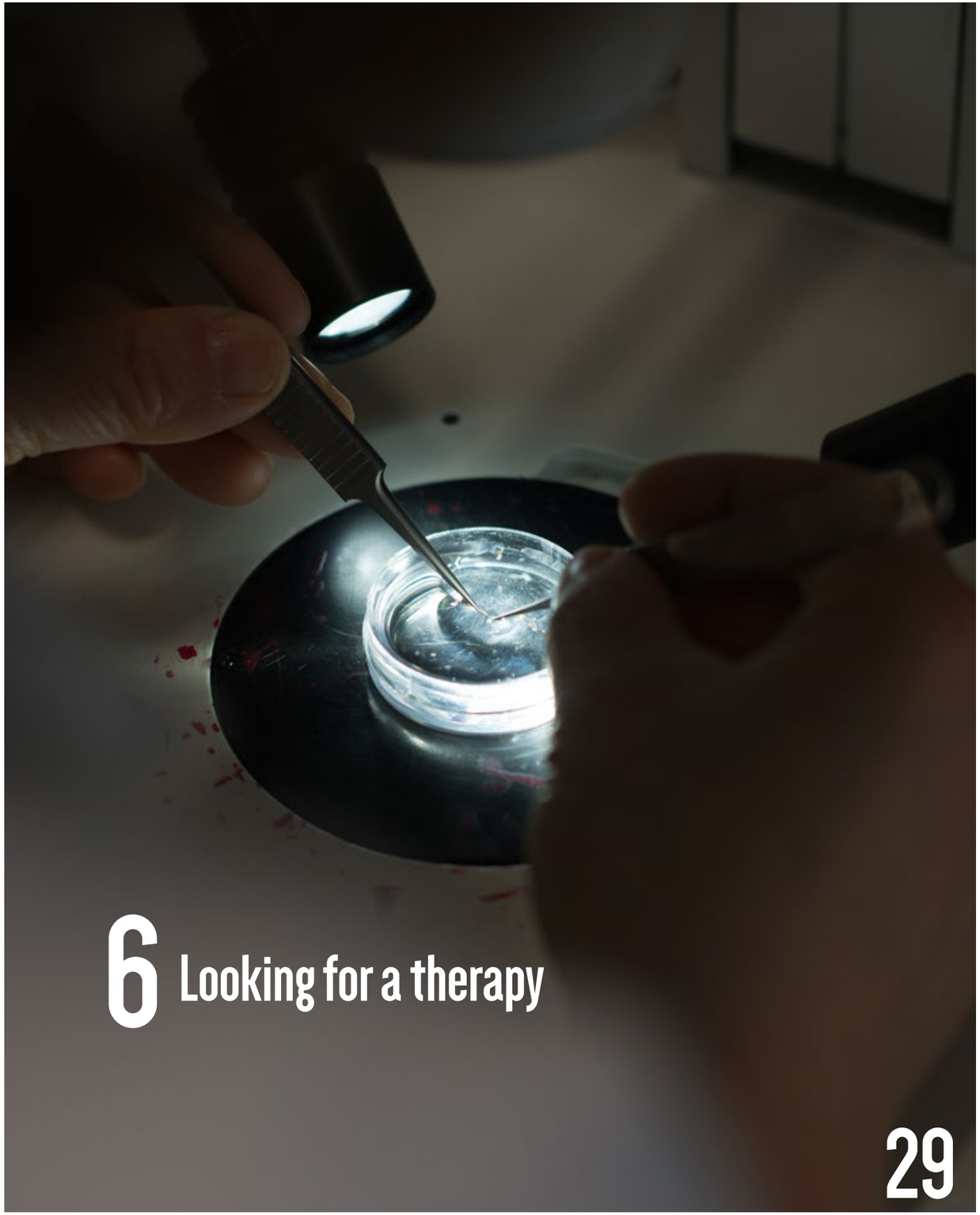
A life with a lot of loss, he calls it. No longer knowing where the pots are. Which is the bicycle key and which is the house key? Not knowing in the afternoon what you've done that morning. Am I in the plane or in the train? ... asked Lots recently when they visited their eldest daughter in the US. Lots has lost her compass in life ... that makes me very frightened, says Joop.

It's been a few weeks since but it's still reverberating after ... our conversation.
It started with Do you still love me, Joop?
I was surprised and said, yes, of course... I wondered: why are you asking this now?
Yes, I change and I'm not sure if you still ...
And I'm going to change even more...
I already knew some fears that Lots had ...
fear of the nursing home,
fear of being very dependent on caregivers,
fear of not being taken seriously,
fear of not recognizing your children.
I thought I knew all her fears ... it seemed to be a lot.... but it isn't.
Fear of abandonment, everyone's greatest fear, is added to the list.

Joop Stam



Alzheimer



6 Looking for a therapy

Existing treatments

Making a diagnosis is one thing, developing a therapy for Alzheimer's disease is something quite different. Nevertheless, there are a number of drugs today that doctors prescribe to their patients with incipient or mild Alzheimer's disease. Firstly, there are drugs that improve the signal transmission between nerve cells. These drugs inhibit the breakdown of the signal molecule acetylcholine. These are inhibitors of the enzyme acetylcholinesterase (AChE-inhibitors). There is also a drug that reduces the chronic over-stimulation of the NMDA receptor in certain nerve cells. This drug is prescribed in combination with an AChE-inhibitor for treating patients with a moderate to severe form of Alzheimer's disease.

There is debate about the efficacy and cost-effectiveness of these drugs. Most international guidelines for doctors recommend these drugs anyway because they would be useful at the beginning of the disease, while others, including the Belgian KCE (Federal Health Care Knowledge Center), state that the efficacy of these drugs is very limited.[47]

The drugs not mentioned above mainly deal with the non-core symptoms of the disease: hallucinations, aggression, passivity, depression, insomnia, behavioral disorders, etc.

The current focus, however, is on interventions that do not involve drugs. These include support for the patient and caregivers in various aspects of life: in performing daily activities, learning to cope with the disease, encouraging exercise and cognitive activities, as well as social and financial support.

Clinical studies

It is clear that for developing new drugs the bar needs to be set higher than for existing ones. We should at least expect that new drugs actually slow down the process of decline or even halt it, resist the cognitive decline and actually improve the quality of life of people with dementia and that of the people around them.

In a second phase, we can try to actually cure the disease. Although it will probably always be a utopian option, especially for patients who are already far down the road to dementia. The brain cells that bear their memories are by then already mostly dead.

There can be no doubt that research teams and the pharmaceutical industry have made tremendous efforts in the search for an effective treatment. More than 80 potential drugs were tested in various phases of clinical research. A dozen have even been tested to the furthest stage of clinical trials, the Phase III studies (see box: 'The development of a medicine').[48] The studies involved hundreds, even thousands of patients. Studies like these have taken many years and have cost hundreds of millions of Euros.

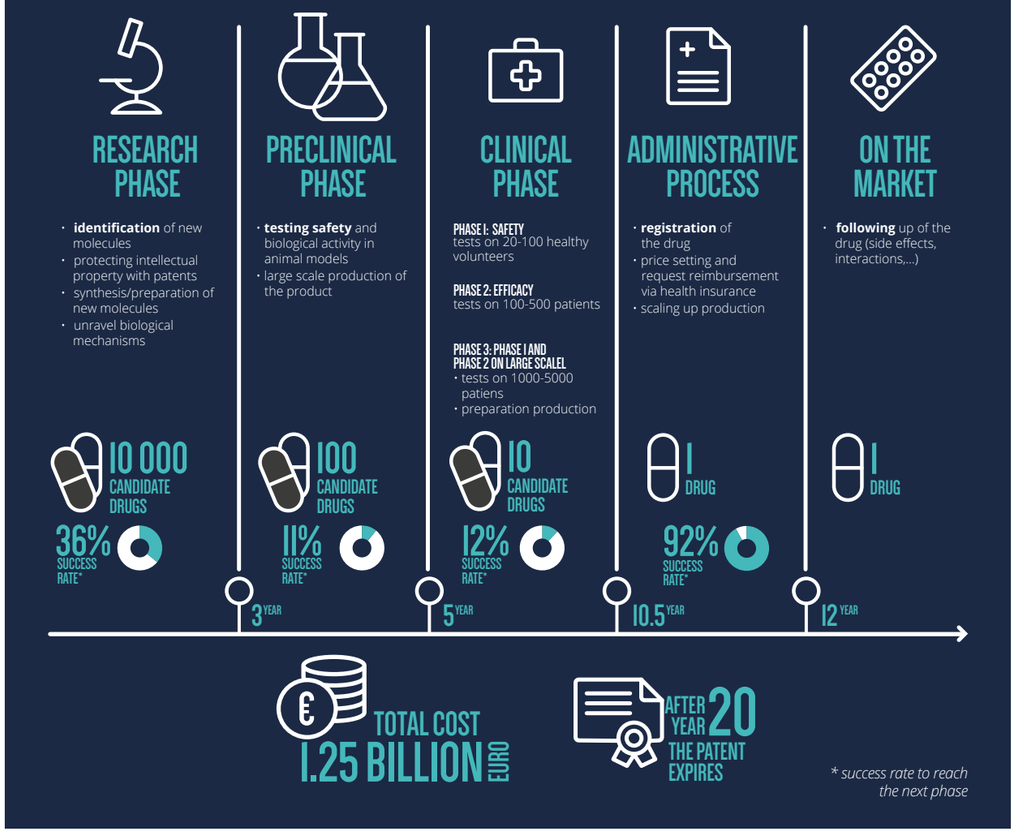
THE DEVELOPMENT OF A MEDICINE

The process for turning a molecule into an authorized medicinal product is long and complex. Before it comes on the market, each candidate drug is tested for safety and efficacy - does the drug do what we expect of it?

This evaluation takes place in clinical trials, which are usually divided into three phases:

- *In a phase I clinical study, the safety is analyzed on a small number of volunteers.*
- *If everything appears to be safe, phase II can start. In this, clinical trials in small groups of patients are used to see if the candidate drug has an effect on the disease to be treated (e.g. patients have fewer memory problems).*
- *If phase II yields promising results, a Phase III clinical study is started. This involves testing the drug for safety and efficacy on a large group of patients. Only when these results are positive can a candidate drug be allowed onto the market by the competent governmental authorities.*

The development of a new drug in Europe takes on average 12.5 years and costs about 1.25 billion Euro.



So far, these clinical studies have not provided the breakthrough that was expected or hoped for. And that is a huge disappointment for not only the patients, their relatives and the doctors and researchers, but also the pharmaceutical companies and governments that have invested many hundreds of millions.[49]

Despite this, these studies were not a wasted effort. On the contrary. They tell us what does not work and what possibly can. These studies can be used to find new directions for tackling this condition.[50, 51] Indeed, for a number of substances the research is being continued, where necessary in the form of a modified type of clinical study. And new molecules and treatments are finding their way into clinical trials. Moreover, we need to learn from other areas of biomedical research. In AIDS research years of clinical trials were needed to find effective medicines and the failures also far outnumber the successes in cancer research. Finding medicines involves a great deal of both trial and error.

The focus in current drug research

Various disease mechanisms are being targeted for developing drugs against Alzheimer's disease.[52]

Aβ production and disposal

At the moment, a whole series of antibodies against Aβ is being tested. One of those agents got into the news because it was not successful in treating a group of patients with mild to moderate dementia. That company concerned now has set up clinical trials that focus on people whose brain damage is still very limited. Other companies are also testing variants of anti-Aß molecules in phase I, phase II or phase III clinical trials in various groups of patients.

Active vaccination

There are also companies that are investigating vaccination. They are developing viruses that carry fragments of the Aß protein. By injecting these (harmless) viruses into the bloodstream, a natural resistance to Aß is generated.

Other companies are trying to achieve the same effect using microscopic fat droplets incorporating Aß fragments.

BACE1-inhibitors

For some years now, there is also been much interest in inhibitors for β-secretase or BACE1. This protein carries out the first cleavage of the amyloid precursor protein (APP) to create Aß (see box 'Plaques with β-amyloid protein fragments'). By inhibiting BACE1, researchers hope to reduce the production of Aß in the brain. Several companies already have BACE1 inhibitors in clinical trials. A number of these studies have already progressed to phase III.

Tau hyperphosphorylation

Furthermore, ways are being examined to limit the hyperphosphorylation and aggregation of Tau (see box 'Tau tangles'). The recent detection techniques based on Tau-PET scanning have led to renewed interest in Tau as a target for developing new drugs against Alzheimer's disease.

Beyond Aβ and Tau

It is also important, however, that drug development is prepared to look beyond Aß and Tau. The section 'Research leads to new insights' argues that the toxicity of Aß fragments and Tau tangles represent only a first step in the disease process (the biochemical phase). It is only in the second, extended and long-term phase (the cellular phase) that we find the run-up to the clinical or true dementia phase.

Drug development also needs to give sufficient attention to this cellular phase. It is therefore not a good idea in developing a therapy to concentrate entirely on one mechanism, such as preventing the accumulation of Tau clusters or ensuring that Aß is processed correctly.

This kind of broader framework is currently being developed. Scientists are looking into how nerve cells under stress can survive longer. How signal transmission between old nerve cells can be improved. How the mitochondria (the energy factories of the nerve cell) can be helped. Or how the equilibrium in the brain can be maintained by means of the astroglia, microglia or oligodendrocytes.

Modified study design

Furthermore, researchers have to be creative in the way they set up clinical trials. The designs of the newer studies have been changed from how they were five or ten years ago.

Support with biomarkers

The diagnosis of Alzheimer's disease on the basis of psychological and cognitive tests lacks precision, as described above. The consequence is that most of the clinical studies up to now have been carried out in a mixed population of dementia patients, and not on a more purified group of people who all actually have Alzheimer's disease. Some researchers estimate that the number of patients without underlying Alzheimer's disease is as high as 30%. New clinical trials are therefore supported with the most advanced diagnostic techniques (including amyloid PET scans and biomarkers - see 'Diagnosis') in order to make the study population as homogeneous as possible. In other studies, the researchers focus on patient populations with a well-specified genetic risk.

A shift to earlier treatment

Even the brains of patients who are still in the early stages of dementia have been subject to Aß production and Tau tangles for at least 10 and possibly even 20 or 30 years. They have in the meantime developed a series of disease mechanisms that we cannot reverse with interventions that counteract Aß or interfere with Tau tangles. It looks as if by the time people develop memory problems and other cognitive symptoms it is already too late for these treatment strategies. We have to treat the problem earlier in order to be effective.

There are other examples in the health sector where early interventions have been fully established. Take, for example, cardiovascular disease: doctors try to prevent heart attacks and strokes by treating people years - even decades - beforehand for high blood pressure and hardening arteries. These people are advised to stop smoking, eat more healthily, exercise more and to take medicines such as beta-blockers and statins.

To successfully treat Alzheimer's disease it may be necessary to use a similar strategy. That is, to intervene before the neurodegeneration begins. That can already be done, at least in theory. After all, provided that further validation becomes available, doctors have the first diagnostic instruments (PET scans and biomarkers) for detecting Alzheimer's disease in the biochemical and/or cellular stage. And these make detection possible years before the first symptoms of dementia emerge.

However, it is obviously not justified to ask healthy people in their fifties and sixties to submit to a PET scan or lumbar puncture and, if they have less favorable results, to treat them with antibodies that neutralize Aß or interfere with Tau tangles in their brains. Nor would it be straightforward to

set up an ethically-defensible clinical study, as not everyone with a less favorable result will go on to develop Alzheimer's disease, 10, 20 or 30 years later. So how do we know whether the medication will work if we don't know what the natural evolution of the disease is in these people? We first need greater insight and predictive markers.

And yet ... there are people at high risk who would be only too happy to participate in such studies (see box 'Gene carriers at the forefront of clinical research').

GENE CARRIERS AT THE FOREFRONT OF CLINICAL RESEARCH

Carriers of certain APP and PSEN mutations (see box 'Genetics supports the amyloid hypothesis') have a very high risk of developing Alzheimer's disease. What's more, they mostly develop the disease at an earlier age.

Several research institutions, the US government and some pharmaceutical companies have united forces to focus clinical research on these patient groups. It involves 'patients' who show no signs of dementia, but who do have a high genetic predisposition for it because they carry a mutation. These are called 'primary prevention studies'.[a]

- *These include the DIAN network (Dominantly Inherited Alzheimer Network), an American, European, Australian research initiative that recruits people with an Alzheimer's mutation to participate in clinical studies.[b]*
- *Another example is the 'Alzheimer's Prevention Initiative' carried out by the Banner Alzheimer's Institute in Phoenix (USA), the US National Institutes of Health (NIH), the Genentech company (Roche) and the University of Antioquia's Grupo de Neurosciencias in Medelin (Colombia).[c] In this study, members of a very large Colombian family are treated with an antibody to Aß. The treated subjects are all carriers of the PSEN1 E280A mutation.[d]*

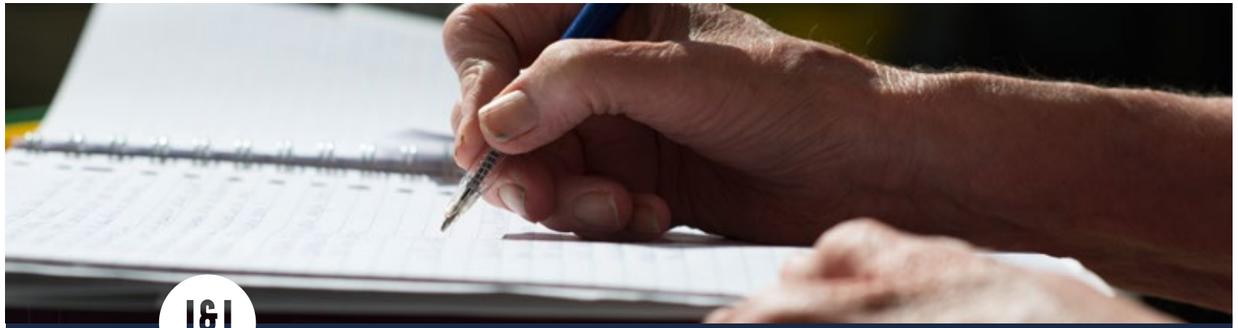
These studies will provide the first results in a few years. Researchers eagerly wait to see whether they can win the race against Alzheimer's disease in this group of patients.

Treating it as a network disease

It is, however, unrealistic to think that we will ever find a magic pill that solves all Alzheimer problems. As has been already said, Aß and Tau are only part of the problem. We will also need to look further and develop a broader treatment that affects the multitude of pathways in different cellular compartments in various parts of the brains so that it can halt the progression of the disease before it can break through.

How we can do that is still unclear. Some researchers talk about a 'multi-target' therapy in the form of a pharmaceutical cocktail, possibly supplemented with vaccination strategies, cognitive therapy and other non-drug treatments Others set their hopes on more futuristic treatments such as gene therapy or cell therapy. But, as far as Alzheimer's disease is concerned, these approaches are still in their infancy.

It would undoubtedly be a major achievement to develop an effective therapeutic mix that is also affordable for patients and healthcare authorities.



If we just keep the connection

Lots and Joop are getting through it together. Support groups and Alzheimer's cafés help them with that. How do others do it? What do we learn from each other? What works and what does not. The disease might be a tragedy, but that doesn't turn a life with dementia into one. Not yet, says Joop. As long as we keep the connection, adds Lots. You have the illness together, and you have to find a way to go along with it. Others can provide help and support. A psychologist, social worker or case manager ... We have a monthly talk with a psychologist. That helps.

The illness has made their relationship stronger. That was strong at the start, but now they are much closer still. A great illness for your relationship, laughs Lots. If we just keep the connection, repeats Joop. This is a mantra that plays constantly in my head.

Lots writes and paints. An entry in her diary every day. To hold onto the memories. With some support from Joop. More and more often. Until recently, she wrote poems. She made a booklet with 'Elevens' - short poems, each with eleven words, about her Alzheimer's. Small, condensed masterpieces.

She paints as well. For that she has to go all the way to Amsterdam. By bike. She prefers to cycle alone. Joop is not allowed to take her. She's firm about that. No matter how concerned he is. She started painting 17 years ago. Before the Alzheimer's. She wants to keep doing it. Lots says: If you draw and paint about Alzheimer's, it becomes true. If you write it down, it becomes less frightening. Then you can forget about it for a bit, and you can let it go.

Do
I know myself?
Do I know
who I am without
thoughts?

Forgetting
sweating inside
words melt away
so gratefully shared
with you.

Lots Stam-Vermeulen

7 What about prevention?

Do we have to sit idly by while waiting for the results of the therapeutic research? Definitely not. It is prudent to act preventively against Alzheimer's disease, says the World Health Organization (WHO). As already mentioned in a previous section, the WHO believes that risk factors for cardiovascular diseases not only increase the risk of vascular dementia, but also affect the risk of developing Alzheimer's disease.[53]

British experts have also recommended a heavy focus on cardiovascular risk factors in the prevention policy for dementia. The Dutch Health Council also recommends giving attention to healthy lifestyles when advising the public about preventing dementia.[54] The Council believes that guidelines for detecting and treating hypertension, diabetes, elevated cholesterol and atherosclerosis should pay attention to dementia.[55]

What's more, some recent studies claim that 30% to 50% of new cases can be prevented from developing Alzheimer's disease by combating six risk factors: diabetes, hypertension, obesity, smoking, depression and lack of exercise.[56, 57]

Even more recently there was an epidemiological study in four European countries - the Netherlands, Sweden, Spain and the United Kingdom - that found that the number of people with dementia may be stabilizing, despite an ageing population. The researchers think this is the result of the healthier lifestyle of adults, especially in terms of cardiovascular risk factors.[58]

Another study showed that dementia is decreasing mainly amongst the higher-educated.[59] The number of new patients declined by 44% over thirty years. A decline that was only noticeable in people with higher education. Studying apparently provides good protection against dementia. Whether that has to do with the extent to which we actively encourage our brains, or the fact that highly educated people have the means and the knowledge to live healthier lives, remains to be seen.

It is in any case becoming increasingly clear that whatever is good for the heart is also good for the brain. And, further, it can't do any harm to build-up the necessary gymnastics for the brain and to remain socially active to ward off dementia and Alzheimer's disease.

Alzheimer

You'll do it!
What a gift!

Lots and Joop keep an eye on the scientific research. Although they are realistic ... I hope that there will be a solution, says Lots. But whether it will help me, I don't know. I know that it will be years before there is a breakthrough for patients. So it might be too late for me. But I think they should keep looking.

Lots and Joop very much hope that they can stay together for as long as possible. Seize the day, has become their motto in life. Because they know there are dark clouds on the horizon. Maybe Lots will have to go to a nursing home, says Joop. We accept that. We talk about it. But I hope it will never come to that.

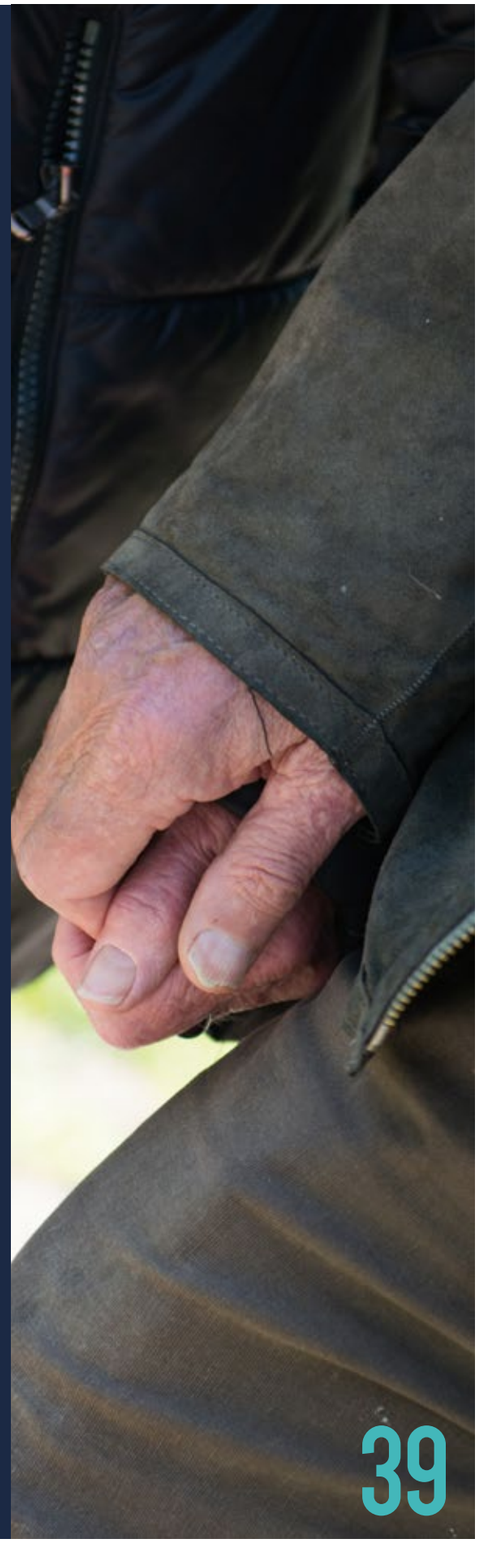
Recently, we were in an Alzheimer's café. We met Dineke there ... had a strong Amsterdam accent ... who lived in a caravan, with a husband who had Alzheimer's: he'd died eight weeks earlier. She told in touching words how he became quite lucid two days before he died. He had used her old pet name, had stroked her hair. And died quietly. A special story. How did you manage to keep him at home? How did you do that? I asked her. You'll manage it as well, she said. I've seen you.

I was immensely moved. What a gift!

Forgetting
and avoiding
are my enemies
they feed my lonely
existence.

I
will softly
whether or not
it is asked of me
be extinguished.

Lots Stam-Vermeulen



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Basic research in life sciences is VIB's raison d'être. On the one hand, we are pushing the boundaries of what we know about molecular mechanisms and how they rule living organisms such as human beings, animals, plants and microorganisms. On the other, we are creating tangible results for the benefit of society.

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