

# Alzheimer's: Will there ever be a cure?

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## PERSPECTIVE

### There is much discussion about Alzheimer's. How serious is the disease?

Quite serious! Over the past few decades, once considered a rare disorder, Alzheimer's has emerged from obscurity to become a major public health problem. To underline the seriousness of the situation, I would like to quote The Honorable Mr. Newt Gingrich, former Speaker of the U.S. House of Representatives. In his Newsletter of 14 February 2018, he wrote:

*"Alzheimer's is the costliest disease in America. From now to 2050, it will cost an estimated \$20 trillion (about the size of the entire national debt). A crash program in brain science would probably do more to balance the budget than any other effort".*

Year-2018 estimates vary, but experts suggest that as many as 5.5 million Americans and 50 million worldwide age 65 and older are living with Alzheimer's and dementia. According to the Alzheimer's Association, every 65 seconds, someone in the U.S. develops this disease. Curiously, according to the Association, Florida is number one in Alzheimer's per capita cases in the U.S.! We have no explanation for this happenstance. Alzheimer's is currently ranked as the 6<sup>th</sup> leading cause of death in the U.S., and 3<sup>rd</sup> just behind heart disease and cancer as a cause of death for older people. With increased life expectancy, the disease will become even more prevalent, resulting in an extremely heavy financial burden on society and its resources. Unless it can be effectively treated or prevented, the number of people with the disease will increase significantly if current population trends continue. However, while increasing age is the most important known risk factor, it is not the cause of the disease. It behooves all of us (patients, their families, and their caregivers; physicians; scientists; and even politicians) to heed the urgency and importance of finding a cure.

Based on a lack of treatment, Alzheimer's has generally been considered an irreversible, progressive brain disease that slowly destroys memory and thinking skills, eventually even the ability to carry out the simplest tasks. It is a chronic neurodegenerative disorder of poorly (or not) understood cause(s). Based on identified risk factors, no less than 18 theories (hypothesis) beyond genetics have been proposed so far for its cause(s). Such a wide array of hypothesis is by itself indicative of our lack of true understanding and knowledge of the disease. In the absence of medical breakthroughs, 152 million people are predicted to develop the illness by 2050 with a worldwide cost projected to reach \$2 trillion by 2030! But the picture is not all grim! Since Alzheimer's was described, we have made strides in research and in the clinic, and these advances should help us progress more quickly toward the goal of finding effective treatments and cures.

### But what is Alzheimer's? and what are its hallmarks?

In 1901, Dr. Alois Alzheimer (a German physician and neuropathologist) first described the disease that now bears his name in a 46-year-old woman (a certain Frau August Deter

whose name has since remained in the medical annals). It is associated with progressive memory loss accompanied by confusion, language problems, and an unpredictable behavior. Five years later, after she died, he examined her brain and saw that it was full of unusual clumps known as *plaques*.

It was only over a century after Dr. Alzheimer's description of the disease that it was determined that the plaques are made of a protein called "amyloid-beta", one of the hallmarks of the disease. The protein comes in several different molecular forms

that collect *between* neurons. It is formed from the breakdown of a larger protein, aptly called "amyloid precursor prot". One such form called "amyloid-beta 42" is thought to be especially toxic. This is the origin of the so-called "amyloid plaque theory". There are many subtle variations of it but, generally

the theory goes that amyloid-beta accumulates in the brain then clumps together. Somewhere in this process, nerve cells in the brain become damaged, leading to memory loss and other symptoms. Thus, it was initially assumed (I must say naively) that the treatment should be straightforward, namely, stopping the clumping of the beta proteins and dissolving the plaques would stop the disease! Unfortunately, such did not prove to be the case. Treatment with such drugs as the plaque-buster *Aducanumab* did arrest the clumping and clear amyloid-beta in the brain as it was supposed to do but, to everyone's dismay, the disease continued unabated and, in some cases, even got worse. In view of such disappointing results, that experiment was prematurely terminated and use of the drug discontinued. As a presumed root cause of Alzheimer's, this theory has failed us and should be abandoned. Unfortunately, and to our detriment, it has erroneously dominated the discourse. In reality, and fortunately, few neuroscientists still subscribe now to the view that it is the amyloid-beta plaques themselves that cause the symptoms of Alzheimer's. Since then, other hallmarks of Alzheimer's have been discovered.

In addition to the plaques, there are three other hallmarks called:

1. Neurofibrillary tangles
2. Chronic inflammation
3. Vascular complications.

These four hallmarks of Alzheimer's are remembered by the acronym **BTIV** (**B** stands for beta-protein; **T** for tau-protein; **I** for inflammation, and **V** for vascular).

The neurofibrillary tangles, the second hallmark of Alzheimer's, are abnormal accumulations of another protein called "tau" that collects *inside* neurons. Whereas the beta proteins accumulate *between* neurons, by contrast, the tau proteins accumulate *inside* neurons. Normal tau is required for healthy neurons, which are in part supported internally by structures called "microtubules". These microtubules help guide nutrients and molecules from the cell body to the axon and its dendrites. In healthy neurons, tau normally binds to and stabilizes the microtubules. But, abnormal chemical changes cause tau to detach from the microtubules and stick to other tau molecules, forming threads that eventually join to form tangles inside neurons. These tangles block the neuron's transport system and harm the synaptic communication between neurons. As a result, neurons fail to function normally and eventually die. As the level of amyloid-beta reaches a tipping point, there is a rapid spread of tau throughout the brain. But this is

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not the whole story! There is a complex interplay between amyloid-beta and tau and perhaps also other proteins.

After the plaques and the tangles, chronic inflammation is the third hallmark of Alzheimer's. It may be caused by the buildup of glial cells (there are two such types of cells called "microglia" and "astrocytes"). These cells are the "housemaids" of the brain. They are normally meant to help keep the brain free of debris. In Alzheimer's, they fail to clear away waste, debris, and protein collections, including the amyloid-beta plaques. They also release chemicals that cause chronic inflammation and further damage the neurons they are meant to protect.

Lastly, vascular complications are the fourth hallmark of Alzheimer's. Atherosclerosis, and mini-strokes They may lead to reduced blood flow and reduced oxygen to the brain, as well as a breakdown of the blood-brain barrier. That barrier usually protects the brain from harmful agents while allowing in glucose and other necessary factors, and its breakdown wreaks havoc.

These are the four hallmarks of Alzheimer's: the amyloid-beta plaques, the neurofibrillary tau-tangles, chronic inflammation, and the attendant vascular complications.

### What happens to the brain in Alzheimer's?

As a result of these four hallmarks (plaques, tangles, inflammation, and vascular complications), the brain is damaged. The damage manifests itself in three brain structures:

1. It initially appears to take place in the hippocampus, which is that part of the brain that is essential in forming memories;
2. The brain structure and convolutions are distorted with extreme shrinkage of the hippocampus and the cerebral cortex; and
3. The ventricles are severely enlarged.

As more neurons die, additional parts of the brain are affected, and they also begin to shrink. By the final stage of Alzheimer's, the damage is widespread and brain tissue has shrunk significantly. The brain typically shrinks to some degree in healthy aging but, surprisingly, does not lose neurons in large numbers. In Alzheimer's, however, damage is widespread as many neurons stop functioning, lose connections with other neurons, and die.

In summary, what happens to the brain during the development of Alzheimer's is multifold:

1. Deterioration of the function and survival of neurons, their networks, and their several key biological processes
2. Breakdown in communication between neurons;
3. Impairment of the metabolism and
4. Impairment of the ability of neurons to maintain and repair themselves, or remodel their synaptic connections, or else regenerate new neurons, which are all important processes for learning, memory and possibly brain repair.

The brain ravages are further accentuated in stages from preclinical, to mild-to-moderate, to severe Alzheimer's. Modern imaging technologies (CT, MRI, PET, and others, either singly or in combination) show the Alzheimer-diseased brain to be a profound modification of a healthy brain with shrinkage of the cerebral cortex and the hippocampus and severely enlarged ventricles. The deterioration from a normal brain is striking! In fact, the extent of brain shrinkage may actually be used as a rough gauge for assessing the severity of the disease. It is also intuitively clear that beyond a certain amount of shrinkage, no drug or treatment could remedy the situation. The ravages of Alzheimer's can be more dramatically visualized in medical images from positron emission tomography (PET) scans.

### Doesn't genetics also play a role in Alzheimer's?

There is a genetic component to some cases of early-onset Alzheimer's (occurring between the ages of 20 to 60), representing less than 10% of the affected people. For example, a child whose biological mother or father carries that genetic mutation has a 50/50 chance of inheriting that mutation. If the mutation is inherited, the child has a very strong probability of developing early-onset Alzheimer's. The genetic component of early-onset Alzheimer's is associated with chromosomes 1, 14, 19, and 21. Mutations on these chromosomes cause abnormal proteins to be formed that have been associated with different forms of Alzheimer's. The mutations on chromosome 19 are the most notorious ones because they lead to the

three well-known variants called Apolipoprotein (or ApoE) 2, 3, and 4. Variant 2 is relatively rare and may protect against the disease. If a person has it, Alzheimer's usually develops later in life than it would have with the other variants. Variant 3 is most common and plays a neutral role, neither increasing nor decreasing the risk of getting Alzheimer's. Variant 4 is the highest genetic risk, however, inheriting it does not mean that a person will develop Alzheimer's and some persons without it may nonetheless develop the disease.

However, the predominant case of late-onset Alzheimer's (from the mid-60 to older ages) affects the remaining 90% of the affected people. We have not found a specific gene that directly causes it. It arises from a complex series of brain changes that occurred over the decades. The causes probably include a combination of genetic, environmental, and lifestyle factors - what I call **GEL** (**G** for genetics, **E** for environment, **L** for lifestyle or the "guilty triad"). The importance of any one of these factors in increasing or decreasing the risk of developing Alzheimer's may further differ from person to person.

### Can asymptomatic people still be diagnosed with Alzheimer's?

Apparently, yes! Low levels of amyloid-beta in the cerebrospinal fluid can predict the presence of Alzheimer's pathology in the brain. Just as low amyloid-beta levels in the cerebrospinal fluid indicate the presence of Alzheimer's, so do elevated tau levels. However, a particular form of tau (the phosphorylated form) is specific to Alzheimer's.

### Are there precursors to Alzheimer's?

Yes! Starting slowly and worsening over time, the most common early symptom is short-term memory loss and confusion, which may be mistaken for the kinds of memory changes that are sometimes associated with normal aging. However, the symptoms of Alzheimer's progress to language problems, disorientation, mood swings, loss of motivation, not managing self-care, behavioral and personality changes, a decline in cognitive abilities such as decision-making and language skills, and problems recognizing family and friends followed by withdrawal from family and society ultimately leading to a severe loss of mental function. These losses are related to the worsening breakdown of the connections between certain neurons in the brain and their eventual death. Gradually, bodily functions are lost, ultimately leading to death. Although the speed of progression of the disease can vary, the average life expectancy following diagnosis is on the order of three to nine years. New York University has provided a functional assessment staging scale (called **FAST**) with an accompanying easy-to-understand pictorial of this progression in seven stages.

### How is Alzheimer's diagnosed? Is there a recommended protocol?

At this juncture in our understanding of the disease, a "gold standard" for Alzheimer's diagnosis has been developed from the systematic testing of the various identified risk factors. However, having assessed these several risks, managing them may have benefits but will not yield a cure. The test results can provide a baseline against which one could gauge the benefits of any treatment followed. Although this set represents an ideal set, not all tests will be ordered by the treating physician for various reasons (not deemed necessary in particular situations; too costly, etc.). In addition to ruling out other diseases, the risk factors are classified under 13 categories:

1. **Genetics:** For early-onset, gene mutations on chromosomes 1, 14, 21. For late onset, ApoE and its variants on chromosome 19
2. **Infection:** brain pathogens (viruses, bacteria, fungi, molds, parasites, etc.).
3. **Inflammation:** A key player (the third hallmark)
4. **Homocysteine:** An amino-acid causally associated with Alzheimer's and brain atrophy
5. **Fasting insulin level:** Inflammatory response caused by sugar toxicity
6. **Hormonal status:** Estradiol, testosterone, thyroid-stimulating hormone, etc.
7. **Toxic exposure:** Mercury, mycotoxins, etc.
8. **Immune system:** A first responder to infections
9. **Microbiome:** Bacteria and other microbes living in the gut, mouth, nose, and sinuses
10. **Blood-brain barrier status:** Impaired integrity allows access to the brain by microbes, viruses, fungi, etc.

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11. **Body mass index:** Measure of overweight condition
12. **Pre-diabetes/diabetes status:** Drivers of Alzheimer's and
13. **Volumetrics:** Brain atrophy.

For each individual, it is also possible to design a set of genetic, biochemical, and other tests that would provide a personalized risk profile for Alzheimer's. These tests will identify those suboptimal conditions according to present health guidelines

that would require attention. Depending on that person's health condition, the number of suboptimal test results will, of course, vary. The tests cover eight relevant areas:

1. Genetics
2. Blood
3. Trophic support
4. Leakage
5. Toxicity
6. Cognitive performance
7. Imaging and various other tests (sleep, microbiome, mitochondrial function, BMI)
8. Related considerations of Patient's family history and lifestyle.

These tests will pinpoint which factors are driving cognitive decline. The list is all-encompassing and may not be applied in its entirety in every case. It also illustrates the multiplicity and complexity of Alzheimer's factors.

In addition, several blood tests have also been proposed:

1. **Blood test # 1 - Sleep molecules:** These sleep-inducing fatty molecules produced in the brain are also found in blood; they are higher in people who have elevated levels of brain amyloid-beta. They are known to be neuroprotective and to induce sleep in line with evidence that amyloid accumulates in the brain with a lack of sleep. The molecules are also connected to brain shrinkage and memory loss and are suspected of playing a role in clearing up toxic amyloid in the brain. A blood test for the presence of these molecules would be cheaper than measuring amyloid in the brain and easier to do than a spinal tap. However, I am not a proponent of such a test as it is premised on the erroneous assumption that amyloid-beta is the cause of Alzheimer's.
2. **Blood test # 2 - Errant proteins:** These are associated with the start of Alzheimer's and can be detected with a blood test.
3. **Blood test # 3 - Quantification of minute traces of amyloid beta:** It is alleged that such traces can be used to gauge the progression of Alzheimer's, allowing identification of people likely to develop dementia over the coming decades.
4. **Blood test # 4 - Plasma amyloid levels:** Similar to blood test # 3.

Further, it is possible to determine whether a person has *possible* Alzheimer's dementia (since dementia may be due to another cause) or *probable* Alzheimer's dementia" (if no other cause for dementia can be found) utilizing an established methodology.

### Can Alzheimer's be predicted?

The eyes are...an ideal mirror of the brain and an early predictor of the disease. Alzheimer's patients have decreased retinal blood flow and vessel density that are also present early in the disease process. So-called OCT angiography can image reduced blood capillaries in the back of the eye, yielding a noninvasive way to diagnose early cognitive impairment.

### Can Alzheimer's be prevented or at least slowed down?

Although scientists have conducted many studies, and more are ongoing, some focusing on drugs, some on lifestyle or other changes, so far nothing has been proven to prevent or delay Alzheimer's and its dementia. But researchers have identified promising strategies and are learning more about what might—and might not—work. Changes in the brain can occur many years before the first symptoms of Alzheimer's appear. This is a possible window of opportunity to prevent or delay debilitating memory loss and other symptoms of dementia.

Emerging evidence that the incidence and prevalence of dementia are declining in some high-income countries offers hope that public health interventions can be effective in preventing cognitive decline and dementia. Further, a growing body of prevention research is emerging. Thus, the (U.S.) Agency for Healthcare Research and Quality has concluded that there was *insufficient evidence* to make recommendations about interventions to prevent cognitive decline and dementia. The (U.S.) National Institute on Aging and the (U.S.) National Academies of Sciences, Engineering, and Medicine (NASEM) concluded that despite "...a wide range of programs and products, such as diets, exercise regimens, games, and supplements, including a combination of the same, it is difficult to ascertain what has been demonstrated to prevent or reduce risk". It further concluded that current evidence does *not* support a mass public education campaign to encourage people to adopt specific interventions to prevent cognitive decline or/and Alzheimer-type dementia. Importantly, however, it cited *encouraging although inconclusive evidence* for the following types of interventions [1,2]:

1. **Cognitive training:** It is *promising* but NASEM *could not draw conclusions about the relative effectiveness of different cognitive training approaches or techniques*. However, it found *no evidence* to suggest that cognitive training might prevent, delay or slow the development of mild cognitive impairment or Alzheimer's; (
2. **Blood pressure management:** There is *encouraging but inconclusive evidence* that blood pressure management might prevent, delay or slow clinical Alzheimer's-type dementia, particularly in midlife. However, it may *reduce the risk of dementia and cognitive decline*
3. **Diet:** Despite its other benefits, diet was *not found to prevent cognitive decline* or Alzheimer's. However, the focus has been on individual foods rather than comprehensive diets so their results should not be taken at face value. Nonetheless, a healthy diet is an important part of healthy aging. It has also been difficult to ascertain the results as they differ between population-based studies and randomized controlled trials. I have reviewed in my book the 11 most promising diets. While conclusions cannot yet be drawn, it would appear that a healthy diet lowers the risk (risk, not cure!) of Alzheimer's and improves outcomes in those with the disease
4. **Increased physical activity:** In addition to its many health benefits, physical exercise offers possibly a reduced risk of age-related cognitive decline, a decreased rate of dementia, and a reduction in the severity of symptoms in those who are already afflicted by the disease. However, there is not enough evidence to recommend exercise as a way to prevent which specific types of physical activity might be particularly effective
5. **Stress:** Studies that try to link stress, cognitive decline, and AD in humans have had mixed results
6. **Sleep:** Restful sleep helps to clear amyloid from the brain and offers an anti-inflammatory benefit, which can further boost brain health. The right quantity and quality of sleep need to be emphasized;
7. **Mental and physical exercises:** They have similar benefits in lowering the risk of Alzheimer's and slowing the rate of cognitive decline in older adults;
8. **Social integration:** It is a powerful predictor of health and longevity. However, more controlled, longitudinal experiments need to be carried out for confirmation. There is limited evidence that other factors than those discussed show a reduced risk for Alzheimer's without changing the duration of the disease including:
  - Lifestyle
  - Education
  - Learning a second language
  - Foods containing flavonoids (e.g., cocoa, tea,..)
  - Alcohol: light-to-moderate (particularly red wine)
  - Caffeine
  - **Vitamins & Supplements:** There is no consistent evidence of any benefit from vitamin A, B<sub>12</sub>, folic acid, D and E, the alpha-tocopherol form of vitamin E, selenium and zinc, minerals and supplements (omega-3 fatty acid supplements from plants and fish or dietary docosahexaenoic acid (DHA).

- **Spices:** No benefit of spices has been shown in humans despite tentative evidence of benefits in animals.
- **Ginkgo or cannabinoids:** Likewise, there is no convincing evidence that they have any positive effect on cognitive impairment and dementia.

The bottom line is that Alzheimer's is a complex disease and it is likely that the best strategy to prevent or delay it may turn out to be a combination of measures. In the meantime, you can do many things that may keep your brain healthy and your body fit.

#### What is the current treatment for Alzheimer's?

I am quoting in part the Alzheimer's Association, which said:

*"...a genuinely new Alzheimer's drug has not been approved since 2003, ... the currently approved Alzheimer's medications are ineffective in stopping or slowing the course of the disease, the four available Alzheimer's drugs may help lessen symptoms such as memory loss and confusion, ... no drug can cure Alzheimer's or stop it from progressing".*

These four drugs are: *Donepezil* (Aricept), *Rivastigmine* (Exelon), *Galantamine* (Razadyne), and *Memantine* (Namenda). A fifth drug *Namzarine* is a combination of Donepezil and Memantine in a single pill.

Further, of the 244 experimental Alzheimer's drugs tested from 2000 to 2010, exactly one – *Memantine* (Namenda), was approved in 2003 as just indicated...and its effects are modest at best. No drug would prevent the disease from developing from earlier conditions (known in the field as "subjective cognitive impairment" and "mild cognitive impairment") to full-blown Alzheimer's, and ultimately to dementia. Also, the most recent treatment (the amyloid-beta plaque-busting drug *Aducanumab*) mentioned earlier produced such disappointing results that its manufacturer was compelled to discontinue its clinical trial prematurely.

As of early 2020, nothing reliably prevents or slows Alzheimer's. Further, of the ten most common causes of death, Alzheimer's remains the only one for which there is presently no effective treatment.

#### What are the hypotheses advanced so far to explain Alzheimer's?

Eighteen hypotheses have so far been advanced, each one as "the" cause of Alzheimer's. Except for the genetic hypothesis that explains the familial form of the early-onset Alzheimer's and some suggested mechanisms for late-onset Alzheimer's, unfortunately, such is not the case. They run the gamut of hypothesis categories: amyloid (amyloid cascade, amyloid-related), neurological (neurofibrillary tau tangles, neurodevelopmental or retrogenesis, neurovascular, neuroinflammation and neuroinfection), toxicity, cardiovascular, viral/pathogenic (viral infection, fungal infection, pathogenic) and others (cholinergic, dysfunction of oligodendrocytes, gum disease, smoking). While all these may be *bona fide* risks, they cannot claim to have identified the root cause of Alzheimer's. The rigorous testing of the pathogenic hypothesis is long overdue. Notwithstanding the several instances of the link between viruses and neurodegenerative diseases, even if a definitive link were established, it may only be correlative and not causal.

The 19<sup>th</sup> hypothesis (dubbed INT for Inflammation, Neurotrophy, Toxicity) is a seductive one in that it claims that Alzheimer's is not a single disease but may be made up of three different syndromes that may require different therapies. Each syndrome may be acting either individually or synergistically with the other two. It may perhaps explain why Alzheimer's predominantly affects the over 65 population. Unfortunately, it is not all-encompassing and has many limitations. Further, claims by its protagonists that the DESS (a modified ketogenic Diet, Exercise; Stress; Sleep) approach, to which it had been tailored down, would purportedly prevent, delay, minimize and even revert the disease cannot be accepted at face value. Its validity, even a limited one, would require careful validating clinical trials.

This author's runaway autoimmune hypothesis (the 20<sup>th</sup>) incorporates some of the valid features of the INT hypothesis, but goes beyond it, including among other things addressing and incorporating its shortcomings. It provides not only a clinically meaningful explanation but also charts curative approaches that are based on appropriate immunotherapeutic concepts and principles that have been demonstrated to be efficacious for other diseases (brain cancers, diabetes, etc). At this stage, it remains a theoretical construct built on sound biological principles, but that is nonetheless in need of validating clinical trials. Further, like for any other immunotherapies, caution must be exercised as certain immunotherapeutic agents have been found to cause some concerning adverse drug reactions. Under certain conditions (no

prior radiation treatment to not to suppress the immune system, minimizing the secretion of chemokines to not adversely alter the immune response, and minimizing if not eliminating any possibility of inducing cancer), stem cell therapy could also be contemplated.

#### Will there ever be a cure for Alzheimer's?

Unless the disease has severely damaged the brain "beyond repair", my answer is "yes"! This will be possible only if two things were to happen:

1. Identifying the root cause of the disease, not merely its signs, symptoms, and risks and
2. Devising and following an appropriate strategy for eradicating that root cause.

I discuss these in great detail in my recently published book "Alzhei...who?" in which I demystify the disease by unraveling its root cause and suggest the needed methodology and approach for a cure.

To better appreciate the situation, allow me to digress briefly by describing succinctly the foundation of Western medicine. It is a symptomatic discipline that aims to identify and treat the signs and symptoms of any given disease. It also aims to minimize the risks of incurring it. It does so by making assumptions, noting correlations and associations with clinically-observed features, and hopefully evidencing the root cause of the disease. In most instances, however, that root cause remains elusive and treatment merely addresses risks and symptoms. This is precisely the case for Alzheimer's because of the failure to identify its root cause despite five favorable circumstances:

1. Decades of research since Dr. Alzheimer's description of the disease in 1901
2. Many billions of dollars spent worldwide in research sponsored by governments and the pharmaceutical industry (Roche, Eli Lilly, Biogen, Eisai, Pfizer, Amgen)
3. The development of many drugs (by last account, more than 400 experimental drugs)
4. More than 255 failed clinical trials; and the
5. Extensive publication of research and other articles on the subject (approximately 149,000 articles as of 2019).

It seems that we have been losing the proverbial forest for the trees and, in desperation, have declared the disease as "incurable". Isn't it clear that our approach to finding a cure to Alzheimer's disease is not working? We can and should do better utilizing all the knowledge we acquired over nearly the last 120 years to unravel what I call the "deep biology" of the disease. Unless we reorient our approach, doggedly pursue the search for its root cause, and methodically eradicate it, the disease may indeed remain incurable. It does not have to be that way and this is precisely what I proposed to do in my research as laid out in my book. Also, let us again remember as I am fond of saying that: "*risk is not cause, risk management is not cure...only symptom palliation*".

#### Does your solution offer a way out of this grim situation?

Should we not first ask ourselves the question: "*What is happening? Have we got the cause of Alzheimer's all wrong?*". I believe so! Instead of remaining focused on the primary endpoint of a cure, the emphasis has for too long shifted to surrogate endpoints even though they had not been clinically demonstrated to correlate well with the disease. And we are continuing along this dead-end path. Thus, in the absence of a cause or a cure, the focus of drug research and development is now shifting to:

1. Brain inflammation (the third hallmark of Alzheimer's)
2. Cholesterol buildup (the fourth hallmark)
3. Tau protein accumulation in patients' brains; and
4. Interactions between *amyloid-beta*, *tau*, and other proteins that correlate with (but not necessarily cause) cognitive decline.

Against this background, I posited that Alzheimer's is a *brain autoimmune disease* that has gone rogue, somewhat like a "runaway effect". It is not, as generally assumed, the consequence of protein deposits such as the so-called amyloid-beta plaques or the neurofibrillary-tau tangles, or even of interactions between these and perhaps also other proteins found in the brain, or of inflammation, or vascular complications. While they have been

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identified from clinical observations, or associations, or even correlations made therefrom... they are not the root cause of the problem. They, and perhaps other factors, are but hallmarks of Alzheimer's, not its root cause. Consequently, basing a treatment on removing these proteins, or treating the inflammation, or the vascular complications however helpful will not provide a cure. Again, "risk is not cause, risk management is not cure, merely symptom palliation". I discussed this autoimmune disease theory and even charted a path to a cure in my book.

This may not be such a far-fetched idea! Remember, type 1 diabetes is also an immune-mediated disease. Because diabetes increases the risk for Alzheimer's, some scientists have even equated it with "brain diabetes". However, I disagree with their suggestion of using insulin nasal sprays as a potential treatment!

### Is Alzheimer's an aged person's disease and how long can one live with it?

Although the risk of developing Alzheimer's increases with age, the disease and its subsequent dementia are not a part of normal aging. I posited that it is due to the increasingly compromised immune system that accompanies many (not all) aging persons. There are also some forms of dementia that are not related to brain diseases but are caused by systemic abnormalities such as a metabolic syndrome in which the combination of high blood pressure, high cholesterol, and diabetes cause confusion and memory loss.

The time from diagnosis to death varies - as little as 3 or 4 years if the person is older than 80 when diagnosed, to as long as 10 or more years if the person is younger.

### Is Alzheimer's disease the same as Alzheimer's dementia?

No! Dementia is a global cognitive decline in which many mental abilities are lost. It ranges in severity from the mildest stage, when it is just beginning to affect a person's functioning, to the most severe stage, when the person must depend completely on others for the basic activities of daily living. The progression from Alzheimer's to dementia is not a given. Not all people who show the clinical signs of Alzheimer's will necessarily progress to dementia in their lifetimes. The causes of dementia can vary, depending on the types of brain changes that may be taking place.

Alzheimer's is a symptom of the later occurring end-stage dementia. Dementia, in general, is not a specific disease but an umbrella term for several different conditions. It covers different types of dementia:

1. Alzheimer's dementia, the most common, which accounts for about 50%-75% of all dementias
2. Vascular dementia (20%-30%)
3. Lewy body dementias (10%-20%)
4. Frontotemporal dementia (10%-15%); and
5. Mixed dementia (10%), and other lesser types of dementia. I discuss these several dementia types in my other book titled "Dementia".

### Can we determine how rapidly Alzheimer's patients may develop full-blown dementia?

Damage from Alzheimer's can be present for years before symptoms appear. It was found that the presence of a particular form of the protein tau in the cerebrospinal fluid is an indicator of Alzheimer's. There is a genetic marker that is linked to elevated tau levels. That marker turned out to be associated with rapid progression of Alzheimer's. People who carry it tend to have higher tau levels at any given stage of the disease than individuals without it.

With advances in brain imaging, we can now spot the indicators of dementia quite early (up to 25 years before dementia symptoms set in). Age is the single biggest risk factor: the younger one develops Alzheimer's; the more likely dementia will occur later. The risk factors are the same as for Alzheimer's but, not understanding the root cause of Alzheimer's, we likewise do not understand the root cause of dementia and are powerless to slow it down. There may be so-called "risk genes" but the process of finding them is slow.

### In the meantime, what can one do about Alzheimer's?

When seeking medical treatment, one can ensure that the following ten key treatment concepts are followed:

1. Begin treatment as early as possible
2. Address as many abnormalities as possible
3. Optimize each abnormality correction
4. For each treatment, address the root cause of the problem targeted

5. Iterate on the treatment
6. Treatment should not be drug-based
7. Treatment usually reaches a threshold effect beyond which the pathogenic process can be halted or reversed
8. Lowering sub-optimal homocysteine levels
9. Restoring insulin sensitivity; and
10. Restoring metabolic flexibility.

### Beyond medical treatment, one should also:

1. Become well informed about the disease (important long-term strategy)
2. Look for teaching programs about the various stages of Alzheimer's
3. Establish a strong support network (e.g., National Institute on Aging's Alzheimer's and related Dementias Education and Referral Center)
4. Begin treatment early in the disease process (may help preserve daily functioning for some time, plan for the future, take care of financial and legal matters, address potential safety issues, learn about living arrangements, and develop support networks)
5. Maintain mental function (by engaging in mentally-stimulating activities)
6. Participate in creative arts therapies (preferably under the guidance of a trained therapist): Painting, drama, dance, and music to help improve the quality of life, each in its way of engaging the imagination
7. Manage common behavioral symptoms preferably with non-drug treatments (sleeplessness, wandering, agitation, anxiety, and aggression)
8. Look for new treatments; and
9. Participate in clinical trials.

### Can I retain my memory?

A new method has recently been reported (March 2020) for enhancing memory retention and brain processes during sleep. It depends on evoking memories via the release of scents in one nostril. The memory consolidation process that takes place in the brain during sleep can be amplified by external cues such as scents, improving the nocturnal 'dialogue' between the hippocampus and specific regions in the cerebral cortex.

Another approach aims to revive working memory in older adults. Working memory is linked to specific neural interactions within and between brain regions. It involves two patterns of neural oscillation - so-called gamma and theta rhythms. A specific form of cross-frequency coupling known as theta-gamma phase-amplitude coupling (in which the amplitude of gamma rhythms is coupled to the phase of theta rhythms) has been observed in the temporal cortex. It is thought to reflect the local processing and storage of memory contents. Using this method, age-related declines in working memory was temporarily reversed, lasted 50 min past the stimulation period!

### Can I improve my cognition?

A new study reported improvement in cognitive function in areas including attention, information processing speed, executive function, in addition to the global cognitive function, all of which typically decline with age. It uses the safe and effective hyperbaric oxygen therapy (HOT), which has been safely and effectively applied in other medical fields. During the procedure, the patient breathes in pure oxygen in a pressurized chamber where the air pressure is increased to twice that of normal air. This process increases oxygen solubility in the blood that travels throughout the body. The added oxygen stimulates the release of growth factors and stem cells, both of which promote healing.

## REFERENCES

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