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CAUSES OF ALZHEIMER'S DISEASE (Alz) AND POTENTIAL REMEDIES

Neuroscience

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ABSTRACT

Late onset Alzheimer's disease (Alz) affects 40 to 50% of older populations of prosperous nations. Advancing Alz eventually renders the afflicted helpless and without memory. Other elders have some reduction in cognition but sustain sufficient capabilities to not be helpless and retain sufficient cognition to live well until their fatal diseases. Despite decades of sound research and as many as 200 clinical trials of putative treatments to halt advancing Alz, all attempts failed to yield an effective medication. Epidemiological research has identified many correlates (risk-factors) of developing Alz. It is posited that an accumulation of the consequences of the various risk-factors is sufficient to induce Alz. Possibly, different combinations of risks can cause sufficient chaos of the brain's physiology to be the conditions starting and advancing Alz. For example, insufficient circulating B-vitamins, manifest as hyperhomocysteinemia, and regularly taking of drugs with severe anticholinergic burdens could cause such wide-spread effects to be a setting condition for developing Alz. Both potential setting conditions can be rectified hence could prevent the development of Alz. Other combinations of risks might be causal and might be treatable, hence preventing Alz.

KEYWORDS

Hyperhomocysteinemia; Anticholinergic Burden; Prevention; Risk-factors; Cognitive Skill; Infections; Polypharmacy

What causes late onset Alz? The most common answer is a combination of biological and environment causes. That explanation and similar ones are true, but not enlightening. Those explanations, by themselves, excludes nothing and specifies everything, i.e., the equivalent of saying Alz is caused by something.

There is a significant correlation between chronological age and the development of Alz. Hence, Alz is caused by aging, case solved. Once again, not enlightening until some germane specifics of the weathering of aging are specified. A goodly portion of persons living in the 9th decade of life have not developed advanced Alz indicating that chronological age, itself, is not *the* salient cause of Alz. Along the same lines, there is an association between sex and the development of advanced Alz, with women succumbing to the disease more than men. The fact that men also develop Alz, suggests something unique to women is not *the* salient cause of Alz.

In addition to age and sex, epidemiologists have identified many other correlates of the development of late-onset Alz. A partial list: a sedentary lifestyle characterized by a lack of regular exercise and poor diet (features such as hyperlipidemia and/or hyperhomocysteinemia), chronic insomnia, lack of intellectual exercise, hypertension, diabetes, clinical depression, smoking (inhaling smoke of burning tobacco or marijuana plants and likely, by the modern way, vaping potentially toxic chemicals), living with large amounts of air pollution, excess intake of alcoholic beverages, mild traumatic brain injury, small strokes, visual, hearing & olfactory problems, and effects induced by taking many drugs concurrently (more on this later). Any one or all of these in various, potentially interactive combinations could, in theory, be *a cause* of Alz at a more molecular level. However, we do not have that data.

A recent PubMed search on Alz yielded 161,880 peer-reviewed articles. During the first three quarters of 2020, 10,541 publications were added to the total. Well-funded research has surely led to greater knowledge of Alz and better understanding of the brain. Despite the advances, there is no effective therapy for Alz to either slow or prevent Alz's insidious loss of cognitive skill. We surely have no remedy for the lost brain-tissue associated with advanced Alz. Seemingly, the only option for managing advanced Alz is improving palliative care. *There is a bright side:* intervening in the earliest stages of Alz, by addressing known risks, may significantly slow or prevent the development of advanced Alz (a major theme of this article).

Hardy (2006) summarized the first hundred years of research on Alz beginning with Alois Alzheimer's presentation of a case manifest by progressive cognitive deterioration accompanied by an autopsy of the patient's brain. The autopsy showed an accumulation of debris in interstitial fluid and dying neurons manifest by tangled proteins. Hardy noted that there have been three periods of Alz research. The 1st: "was the definition of the disease by clinicians and pathologists." The 2nd: "the neurochemical work, which led to the identification of the cholinergic lesion in the disease." The 3rd: "is the molecular biological and molecular genetic approach to the dissection of the pathogenesis. This last era of Alzheimer's research has paralleled work on other neurologic and psychiatric diseases and undoubtedly holds great promise both for dissecting disease pathogenesis and for developing mechanism-based therapies. However, it has to be acknowledged that no therapies for any neurologic or psychiatric disease have, as yet, been developed by this approach" (p. 8).

Unfortunately, it has to be acknowledged there are no therapies developed by the molecular, genetic approach, circa 2021, stopping the progression of Alz.

There is a well-developed theory of Alz specifying in some detail a potential causal factor, i.e., the amyloid beta (Ab) theory of Alz (Glenner & Wong, 1984; Selkoe & Hardy, 2016). We now know Ab is a product of enzymatic cleavage of a large protein (the amyloid precursor protein, APP) which is, in turn, a product of the APP gene. Also, Ab is seemingly produced continuously (or nearly continuously, rate of production is probably unknown) and is a prime constituent of toxic plaques of tangled proteins in interstitial fluid of the brain. Ab's normal function is not fully determined (although there are literally hundreds of articles germane to the issue). A theory, with considerable support, posits that Ab binds to intruding debris or microbes floating in the interstitial fluid of the brain hence providing an immune function (Weaver, 2020; Moir et al. 2018). However, there must be mechanisms to remove any complex of Ab with debris. Routes for removal may be the lymphatic systems associated with the dura mater (Louveau, et al., 2015; Aspelund et al. 2015) as well as the lymphatic system associated with the base of the brain and neck (Ethell, 2014). In early onset Alz, buildup of Ab is believed to be a heightened production of Ab leading to excess Ab. In late onset Alz (by far the most common form), likely, but not surely, it is not an excess production of Ab, compared to normal for young ages, but a sluggish removal of Ab from the brain's interstitial fluid allowing Ab to readily combine with other Ab and other materials.

The accumulation of Ab leads to clumps of tangled protein, known as amyloid plaques. These plaques might elicit immune responses not capable of removing the plaques. An initial failure of the immune system-circulatory system to remove the plaques can lead to enhanced immune system involvement and secretion of excess cytokines killing adjacent cells, i.e., inflammation (Weaver, 2020). The debris from dying cells adds to the materials to be removed and adds to immune system's activity. So, the modern amyloid beta theory of Alz does specify a set of events germane to the development of Alz or perhaps a salient cause of Alz. The Ab theory has guided the development of drugs designed to modify an accumulation of Ab and amyloid plagues. In brief, there have been more than over 200 clinical trials assessing various drugs, and all have failed. A salient issue, therefore, is what is the best way to avoid a build-up of Ab leading to Ab plaques in interstitial fluid.

Alzheimer also found tangles within apparently dying neurons. We now label the tangles neurofibrillary tangles of tau proteins. Again, there is a vast literature on this issue (a PubMed search for Tau protein and Alzheimer's disease yields 15,298 germane articles. A brief scan of the literature indicates many issues remain, see Naseri et al. (2019) for a review.

Given no drug to stop the progression of Alz, once there is a marked loss of cognitive skill, attention has turned toward preventing the disease. The following supports prevention is possible. (a) There is not an abrupt start to the disease. (b) The disease progresses slowly at first as manifest by a rather slow loss of cognitive skill indexing a slow progression of brain damage. (c) Many correlates of advanced Alz are signals of ill health for which preventive steps, if engaged well, have yielded salutary outcomes. For example, early onset diabetes, a risk-factor for developing Alz, can be controlled by specific diets and losing bodyweight. Also, a consensus confirms that regular programs of physical exercise sustain health and prevents diseases of all kinds. (d) There was a 2-year attempt (Ngandu et al., 2015) to see if preventive steps (improving diet, exercise, cognitive training & vascular risk training) were programmed that the interventions may reduce the risk of developing Alz. There was a small improvement over control conditions.

Within the context of prevention, there are several approaches. One, use the same drugs tested previously, but now, given earlier or in different doses. Also, there are attempts to develop new drugs or nutritional supplements useful in stemming early developments of the disease indexed by risk-factors. The approach getting the least attention is a behavioral approach, i.e., getting individuals to change their risky habits to healthier ones. The behavioral approach is based on the accepted theory called brain plasticity, i.e., regularly engaged behaviors can shape the physiology, and even induce small changes in the anatomy, of the brain, to be more efficient at what is done regularly. And in so doing can achieve benefits or harms. The behavioral approach surely takes more time and poor habits are often difficult to modify but the behavioral approach has few of the common side-effects of drugs and has been shown to be more effective than available drugs with respect to major risk-factors, for example, chronic insomnia (Morgenthale et al., 2006; Qaseem et al., 2016; Mimeaulat & Morin, 1999).

An example of a biologically informed cognitive behavioral approach is based on the theory that efficient fluid-flow throughout the brain would regularly clear Ab and other debris sufficiently to prevent Alz (like what happens when young). Efficient fluid-flow throughout the brain can be achieved via regular physical exercise, a good night's sleep, and a diet promoting a healthy cardio-vascular system. These healthy behaviors, favorably interacting with one another, are likely to prevent an accumulation of Ab in interstitial fluid of the brain, hence preventing a posited cause of Alz. The behavioral approach depends on citizens engaging healthier behaviors while they have the cognitive skills to do so.

It has been posited that focusing on reducing many salient risk-factors associated with the development of Alz might be therapeutic (Ethell, 2014). Along those lines, it was posited that using the technologies of biologically informed cognitive behavioral therapy (CogBehT) could reduce selected risks hence preventing instances of Alz or, at least, slowing the disease's development (Reid et al., 2017).

There are salient differences between prescribing a developed drug to an elder citizen compared to using CogBehT to nudge citizens to engage activities likely to reduce the development of Alz. The citizen prescribed a drug is a passive recipient expecting the drug to do the work, i.e., often expecting a reorganization of the central nervous system from some stage of ill health to one of health (yes, a grandiose expectation). Whereas CogBehT depends on efficiently urging a citizen to be actively engaged in making behavioral changes likely to induce physiological changes that do not involve a radical, abrupt reorganization of the brain for purported better health but by changes integrated within the normal workings of the brain. For example, changing bad habits such as eating unhealthy meals to gradually eating health-promoting meals and in so doing probably developing an appetite for healthier selections.

CogBehT for chronic insomnia often takes weeks of guided behavioral changes to overcome insomnia. Alternatively, the prescription of sleeping pills (e.g., one of the benzodiazepines or OTC sleeping pills using antihistamines) do induce drowsiness sufficient to aid falling "asleep" on initial usage. However, the side-effects of these drugs are harsh. For examples, the benzodiazepines interfere with the regular rhythm of NREM and REM sleep throughout the night (which produces daytime drowsiness and reduced cognitive and motor skills); benzodiazepines can interfere with the consolidation of learned material acquired during previous wake-time; benzodiazepines are synergistic with ethanol often leading to profound toxicity, particularly to the liver. These sleeping pills do facilitate losing consciousness associated with falling "asleep" but do not promote ordinary healthy sleep. The pills provide a sense of being effective because they initiate an initial loss of consciousness characteristic of sleep; nevertheless, they interfere with functionalities of ordinary sleep.

A disturbing consequence emerges from an analysis of health-care records indicating that bouts of prescribed sleeping pills are related to increases in all-causes of deaths, including such as cancer and cardiovascular diseases. Those taking the pills and those not taking the pills die of similar causes, but those with a history of prescribed sleeping pills get diseases earlier and die sooner (Kripke, 2016a, 2016b & 2016c). The same drugs used to correct insomnia are also widely used to treat anxiety disorders, with the same set of side-effects, because they are nearly the same. I address the issues of the OTC pills for insomnia using antihistamines later.

There is considerable research comparing drug-based versus CogBehT approaches for treating chronic insomnia which has led to both representatives of the medical and psychological communities to come to a consensus view that CogBehT for insomnia is the superior treatment and should be used first (Brasure et al., 2016; Qaseem et al. 2016). A problem: there is a shortage of behavioral therapists specializing in treating insomnia. However, behavioral therapy can be effectively delivered over the internet and even by following instructions in self-help books on the science of sleep. Behavioral technologies plus the natural drive to sleep seem to achieve the positive outcome of a return to a healthy pattern of daily sleep which, in turn, facilitates regular cleansing of the brain of such as an accumulation of Ab and hence reducing a risk of developing Alz (Nedergaard, 2013). Healthy sleep is synergistic with a pattern of regular exercise and a nutritious diet. Yes, a true but hollow overgeneralization unless there are known specifics about what constitutes healthy regular exercise and specifics of what is a nutritious diet (more on these later).

The known solution is "prevention is the best medicine." That approach is true but, like other overgeneralized truths, is hollow unless there are developed ways to have citizens engage preventive activities of sufficient scope to achieve fewer instances of Alz.

Comments on the Lancet Commission's Work on Preventing Dementia

The Lancet (the organization of the famous medical journal) established a Commission on Dementia Prevention, Intervention, and Care. They issued their 2020 report. They make this opening statement: "It is never too early and never too late" to engage dementia-prevention. As of now, once an individual's Alz has progressed to the stage of considerable loss of cognitive skills, it is probably too late to prevent the further progression of Alz. Prevention is best done by correcting salient risk-factors with vigor while individuals have intact cognitive skills, i.e., having the ability to execute preventive behaviors. Further, it is wise to correct salient risks for Alz during the 5th decade of life; however, correcting salient risks at any age may be salutary provided that Alz has not advanced beyond the point of no return.

The Lancet commission's 2020 report added three new risks associated with the development of Alz to the nine previously identified. The new risks are excessive alcohol consumption, head injury, and air pollution. They previously identified: less education, hypertension, hearing impairment, smoking, obesity, depression, physical inactivity, diabetes, and infrequent social contract. Notably missing from the list is chronic insomnia (addressed above).

Diabetes and obesity are modifiable for the better by regularly consuming specific diets and avoiding others. There is significant research on what is a better diet for brain-health (Morris et al., 2015; Omar, 2019) which is compatible with diets preventing cardio-vascular diseases and diabetes. In brief, the better diets are called

Mediterranean Diets featuring fruits, vegetables, whole grains, olive oil, nuts, and legumes, and a marked reduction in intake of animal fats, sugar and sugary foods, and excess salt. Given the research supporting the Mediterranean Diets, there is literally a flood of easily accessible websites, cookbooks, and advertisements on Mediterranean Diets. There are also recommendations for controlling diabetes, obesity and sustaining being healthy called Keto Diets. Both the Mediterranean and Keto diet-plans recommend markedly reduced carbohydrates than usually taken by many citizens; both recognize the need for plenty of protein, but they differ with respect to the intake of animal fats in the diets. All recognize that fats are critical and the utility of some animal fats in what is called a good diet for health, but the Mediterranean Diet recommends a marked reduction of animal fats in favor of plant-based fats.The Keto Diets stress the value of animal fats. All diets recommend, for obvious reasons, adequate supplies of essential vitamins, minerals and a supply of fat, carbohydrates, and protein in a diet. There is research, e.g., Omar (2019), indicating that an optimal diet for prevention of Alz would focus on the use of olive oil as a source of the supply of fats in the diet. Additionally, there are successful commercial programs providing counseling on diets (e.g., WeightWatchers uses proven methods to achieve considerable success).

There are governmental and commercial programs counseling on how to establish the habit of **regular exercise.** There are excellent books advising on optimal regular physical exercise programs for older citizens (e.g., Owen, 2016). Consequently, if more individuals' diets were managed more efficiently and if those same individuals could sustain a program of exercise, there would likely be a significant reduction of Alz. Science-based instructions and counseling on how to achieve better diets and programs of regular exercise have been shown to have positive effects. Yes, there are actions an individual might engage to dimish risks of a progression to Alz and eventually dementia. Further there is help available, often at little or no cost. However, *the public has not been told well-enough that older citizens can, by their own behavior, substantially reduce their risk of developing Alz.*

The Commission did not address hyperhomocysteinemia (Hhcy) signaling a major dietary deficiency, i.e., markedly reduced B-vitamins in circulation. Nevertheless, Hhcy is an independent risk-factor for Alz (Guo et al., 2019; Kennedy, 2016). The B-vitamins are involved with numerous physiological functions; hence depletion of B-vitamins has widespread disruptive effects and symptoms of disease (Kennedy, 2016).

Many citizens' modern diets do not provide enough circulating B-vitamins to have good nutrition. This lack is indexed by blood tests measuring the amount of the protein homocysteine (Hcy) circulating in blood. Hcy is an intermediate product in the metabolism of the essential amino acid methionine. A deficiency of folic acid, B-12 and B-6 inhibits the breakdown of Hcy therefore increasing Hcy concentration. The accumulation of Hcy (i.e., Hhyc) indexes a deficit in circulating folic acid, B-12, and B-6 and likely the other B-vitamins as well. Any blood test indexing over 10 micromol/liter of Hcy in circulating blood increases the risk of cardio-vascular diseases, Alz and all-causes-mortality (Clarke et al.,1998; Stranger et al., 2004). Some set less than 15 micromol/liter to be toward the healthy status. Cardiovascular diseases are major risk-factors for the development of Alz. There is a direct relation between higher levels of circulating Hcy and greater risk of disease. There is reasonable certainty that regular, large-dose-intake of the psychotropic drug ethanol poisons some of the usual processes of digestion hence hindering a sufficient supply of B-vitamins.

The above two paragraphs present a cogent theory. Obvious predictions stemming from the theory posits that supplements of B-vitamins should lower Hhcy-levels to heathy levels. Beginning in 1963 and accelerating in the 1990s, there has been continuous research associated with Hhcy. A PubMed search on Hhcy yields 8,897 articles up to mid Dec 2020. A goodly portion of that research was directed toward whether B-vitamin supplements prevented or lowered Hhyc or mitigated symptoms of diseases correlated with Hhcy or if supplements of B-vitamins would prevent disease onset or early progression of disease.

The outcome of the bulk of the research on the efficacy of supplements of B-vitamins generally failed to indicate that the supplements were effective in preventing or correcting disease. For example, the 2018 assessment by researchers of the Cochrane library (Rutjes, et al., 2018) concluded with this statement: "We did not find evidence that any vitamin or mineral supplementation strategy for cognitively healthy adults in mid or late life has a meaningful effect on cognitive decline or dementia, …" (p. 1). This is concordant with the many previous reviews assessing the effects of supplements of one to three of B-vitamins (Kennedy, 2016). Given the abundance of assessments involving one or up to three of the B-vitamins, the conclusion might be drawn that B-vitamin supplements are probably useless in preventing Alz. Also, there is confusion as to how Hhcy is correlated with so many diseases. However, other perspectives are highly relevant.

Wernicke encephalopathy and Wernicke-Korsakoff syndrome are induced by a severe deficit in thiamine (B1) and such is particularly toxic to the mammillary bodies of the hypothalamus (Osiezagha et al., 2013). The mammillary bodies are a critical part of a circuitry associated with memory with significant interactions with the hippocampus. The symptoms of Wernicke encephalopathy are confusion, ataxia including leg tremor, nystagmus, eye lid drooping and can be misdiagnosed as ethanol-induced drunkenness or withdrawal symptoms due to reduced ethanol circulating. Wernicke's disease can progress to coma and death. As with other B-vitamins, B-1 is not synthesized in the body hence derived from food. A major cause of reduced circulating B-1 is ethanol interfering with the transfer of thiamine from food to circulation.

The prime treatment for Wernicke's is large doses of thiamine administered periodically during a day and for at least 18 days. Given that a thiamine-deficiency is a common side-effect of surgical treatment for obesity; hence, if bariatric surgery is part of the history of a presenting patient, large doses of thiamine are surely appropriate. Untreated Wernicke's disease often manifests as a near permanent, complete loss of long-term-memory, a state named Wernicke-Korsakoff syndrome. The loss of long-term-memory often leads to considerable confabulation (the above two paragraphs' statements are verified by Sarayu, V.; Kumar, A., 2020, National Center for Biotechnology Information, USA).

The use of thiamine-treatment to limit the neural damage proceeding from the early signs of Wernicke-Korsakoff is contrary to the overall idea that vitamin-supplements are not effective. However, this one instance does not negate the overall findings showing no salutary effects due to interventions of B-vitamins.

Kennedy (2016) detailed salient circumstances and in so doing generates new perspectives on Hhcy. (a) The eight B-vitamins work in concert, i.e., their effects are interactive. (b) With respect to brain-health, there are few studies assessing the effects of supplements containing all eight of B-vitamins. (c) Given that B-vitamins are water-soluble any excess vitamin is probably eliminated via urine, hence there is little worry about overdosing and providing essential nutrients are unlikely to produce aversive side-effects. (d) Given that B-vitamins are generally removed from circulation rather quickly via urine and there is little storage of the vitamins, it seems optimal to ensure a continuous supply of all 8 B-vitamins. It follows, research programing only a few days of supplements of few B-vitamins is not likely to restore the health of neuronal structures such as the mammillary bodies. Kennedy (2016) called for research featuring the combined effects of administering all eight of the B-vitamins.

If an individual is getting sufficient B-vitamins via an adequate diet, the addition of some B-vitamins, as a supplement, does not protect against future cognitive decline (Kennedy, 2016). This is reasonable since there is little storage of the B-vitamins and any excess is merely eliminated via urine. Note, as Kennedy (2016) stated the B-vitamins work in concert with one another and hence when supplements of only one to three of the B- vitamins are assessed, the likely outcome will not show the hoped-for benefits. However, there is research indicating when there is Hhcy (i.e., a functional deficit of B-vitamins) that supplements do have beneficial effects (Kennedy et al., 2010; Kennedy 2016 and multiple references therein).

Research with rats involving injections of the protein Hcy, hence producing Hhcy, was shown to induce greater circulating Ab in brain. Guo et al. (2019) replicated the findings that injections of Hcy enhanced Ab in brain. Guo et al. (2019) even found high amounts of circulating Hcy induced considerable Ab floating in eyes of the rats so treated. Also, doses of B-vitamins reduced the amount of Ab

circulating in brain and eye. This line of research provides evidence of a causal relationship between a dietary insufficiency, manifest by Hhyc, and the induction of processes associated with Alz.

It appears we have at hand, easily available a preventive step having profound consequences including better cardio-vascular health and preventing serious diseases of the brain including Wernicke-Korsakoff syndrome, Alz, and a host of other diseases. The process of prevention might begin with regular blood tests for Hhcy and if they indicate Hhcy to urge citizens to take a supplement containing all B-vitamins which are easily available in the retail market, inexpensive, and even in slow-release form. Further, it would make sense to give somewhat larger amounts of B-vitamins than the amounts recommended as minimal standards for health, i.e., "overdose" on all B-vitamins (Kennedy, 2016) and some available supplements do that. Because elder citizens and particularly elderly women are at high risk for developing Alz, it seems prudent to urge them to take the all-B-vitamins-formulations even without a blood test for Hhcy. There is little risk in taking a supplement of B-vitamins which merely corrects any dietary insufficiency. It should be noted that providing a supplement of all 8 of the B-vitamins is a novel approach (developed by Kennedy, 2016).

Nutritionists have identified not only the B-vitamins as missing in regular meals of many citizens, but other essential vitamins and minerals are missing. Among those, for example, is a deficit in the mineral magnesium. Also, there is likely to be insufficient choline in ordinary diets and such is basic to synthesizing the ubiquitous neurotransmitter acetylcholine. There are supplements providing choline for synthesizing acetylcholine; however, there can be too much choline as a supplement. There are meaningful differences between taking nutritional supplements to sustain an optimal diet for health and well-being compared to taking a drug designed to modify some feature of a neuronal system of the brain, e.g., acting as an agonist or antagonist at receptors for a major neurotransmitter (e.g., benzodiazepines, barbiturates, and ethanol as agonists at GABA receptors, hence producing wide-spread deleterious effects). Or a drug affecting an enzyme critical to a phylogenetically old neuronal system that is typically functional (for a germane example, drugs designed to modify the breakdown of the APP protein).

The Commission identified the behaviors of **excessive consumption of alcoholic beverages** as a risk for developing dementia (a dietary & polypharmacy problem). The psychotropic drug ethanol is the active ingredient of alcoholic beverages. Small doses of ethanol taken only periodically are not poisonous and can produce a sense of satisfaction (positive reinforcement and some relief from negativity as well). Those small doses' comforting effects, when experienced frequently, can induce a strong appetite for alcoholic beverages and when that appetite is seemingly out of control there is disease, once called alcoholism, now, excessive consumption of alcoholic beverages or alcohol use disorder. Ethanol is poisonous when taken in exceptionally large doses and when taken in medium sized doses regularly. This is not the place to detail all the poisonous effects induced by alcoholism, see Kamat et al. (2016) for an extensive list of harms. The focus here is on the effects directly effecting the circuitries of memory (e.g., insufficient B-vitamins in circulation engendering Wernicke's pathology). Worthy of note, ingestion of ethanol is more poisonous to women than men due, among other situations, less processing of ethanol in the stomach (Reid & Reid, 2018).

An extensive body of research indicates one of the brain's opioidergic systems is associated with sustaining consumption of rewarding food and drink (Reid, 1990). In studies using rats, it was initially found that small doses of morphine (not sufficient to induce analgesia) regularly increased rats' intakes of an alcoholic beverage and that naloxone or naltrexone, opioid antagonists, reduced intakes compared to previous intakes (Reid & Hunter,1984). Those observations were then verified many times under a variety of conditions (Hubbell & Reid, 1990). The data from the study of rats' intake of alcoholic beverages provides support for the use of naltrexone, the long-acting opioid antagonist, as a pharmacological adjunct to other extant treatments for alcoholism. Naltrexone is effective in reducing craving for alcoholic beverages and in reducing intakes of alcoholic beverages. The opioidergic system associated with ingestion seems to have the function of sustaining ingestion once begun ensuring a full meal. However, when the ingesta is an alcoholic beverage the enhancement of ingestion once begun can be deleterious.

Research (Reid, M.L. et al., 2001) with rats studying their developed large intakes of alcoholic beverages in which naloxone was given for three days and then without for three days and doing that regimen multiple times showed this remarkable effect: with naloxone little intake of alcoholic beverage and without naloxone a return to drinking at nearly the same volume as before the manipulation (intake manifest as obvious drunkenness). It was like turning on a light-switch, injecting modest doses of naloxone reduced intakes, and then when given placebos, we observed a full return to drinking. These observations indicate that psychopharmacology for mental health problems may be, at best, merely a setting condition for cognitive behavioral therapy. For alcoholism, use of opioid antagonists for the treatment will often be only a temporary fix. Use of naltrexone can be helpful in demonstrating that control of drinking is achievable and an opportunity to engage other behaviors. Naltrexone-treatment will be more effective when accompanied by training (self-training or guided training) to change a lifestyle for the better and perhaps training via computer-assisted game-like programs to improve impulse control and sharpen cognition in general (Reid, 2015).

There are salutary public health measures that can be instigated. One particularly effective measure would be to increase the taxes on alcoholic beverages which tends to decrease consumption and hence reduce the risk of diseases and accidents leading to head injuries (Reid & Reid, 2016).

The Commission labeled one risk-factor as **less education**. Although there is a correlation between level of formal education with the incidence of Alz, it may not be the critical feature of a risk. The critical feature maybe the lack of intellectual exercise, i.e., lack of engagement in self-education and little exercise of cognitive skills (computation, problem-solving, regular reading of texts, maps or graphs, regular writing). Neuro-vascular coupling directs blood-flow to areas of the brain having high levels of activity and less blood flow to areas of low activity; a necessary feature because if the entire brain received the same amount of blood-flow as areas of high activity, then the total blood flow would be too great and literally squash the brain against the solid skull. Perhaps, when intellectual cognitive activity is not often engaged, there are areas of the brain that regularly receive less blood flowing in the arterioles, hence providing less oxygen and nutrients.

There have been attempts to compensate for less education by encouraging such as doing crossword puzzles and listening to lectures and taking tests on the content of the lectures. Such activities have not seemed to have any beneficial effects. However, computer-assisted game-like programs designed to exercise cognitive skills do seem to be somewhat effective in slowing the cognitive decline. The company Posit Science, under the leadership of Michael Merzenich (2013) has done well-designed research indicating that cognitive training can be effective in slowing cognitive decline as one ages., The company has compiled about 150 articles showing some benefit in slowing cognitive decline. They market a product called BrainHQ. There are companies, other than Posit Science, whose cognitive-enhancement-products have not been tested adequately to know if their advocated programs are effective. There are a spat of studies showing that playing recreational computer games regularly might enhance cognitive skills. I posit that if programs focusing on reducing the risks of Alz engaged better diets, regular physical exercise, and did the exercises of BrainHQ that would be a step toward preventing Alz.

There is little one can do, if you live in an **air-polluted environment** (particularly if you live next to a heavily trafficked major highways). You can, however, buy an inexpensive, efficient air-filter for your bedroom (a place you may spend a third of your life). Air filters for many workplaces would be of benefit as well.

Another public health risk is the rise of the vaping-industry which has been involved with inhaling products that should never be inhaled (such as synthetic THC and multiple potential toxins in flavorings). This new potential assault on health should be carefully regulated (risks encompassed by the titles **smoking** and **air pollution**). There are efforts to control the marketing of these products, e.g., the recent health-care directives made by Governor Cuomo of New York, USA.

Losses due to reduced fidelity of major sensory systems are major risk factors associated with the development of Alz. The Commission listed **hearing impairment** as a risk for developing Alz, but also could have listed **visual problems** as a risk (Guo et al., 2019). There are

physical aids to correct hearing and visual problems which sustain the fidelity of sensory perceptions. Under the direction of psychologist Aaron Seitz, his team is developing computer-assisted game-like programs to improve vision and hearing (see, Weir, 2021). Posit Science has marketed such programs to improve hearing.

The Commission did not list **hyposmia and anosmia** as risks even though Alz may begin in the periphery of the olfactory brain (Attems et al., 2005) and loss of olfactory perception is an early sign of eventual development of Alz and dementia. The most prevalent cause of lost olfactory perception is lingering effects of infections. A procedure involving sniffing exercises restores some of the loss of olfactory perception but is only effective with about half of the individuals that do the sniffing exercise (Altundag et al. 2015). However, that improvement is far superior to not attempting any program to restore lost olfactory perception (more on olfaction in the discussion of polypharmacy).

The Commission could add **hip fractures** (the fracture and hip-replacements induce great stress) along with **head injuries** as major risks among the elderly due to falls and other accidents. Incidences of accidents are increased by the prescription of drugs inducing dizziness, and reduced motor control, e.g., benzodiazepines. Drunkenness due to ethanol-intake enhances chances of accidents (and, of course, all know this).

The Commission did not engage the idea that **infections could be a cause of Alz**, however, they could have. There is a consensus statement (Itzhaki + 32 coauthors., 2016, and with 79 germane citations) reviving older theory indicating a cause of Alz is the invasion of microbes (probably viruses) into the brain which, in turn, can cause runaway inflammation whose effects can kill healthy cells surrounding a source of infection (Wang et al., 2015). The debris of dying cells also contributes to inflammation hence inducing a march of increasing neuronal death.

A likely place for infectious material to enter the brain is via the foramina of the cribriform plate, the channels for the filia of the olfactory nerve to enter the olfactory bulb. The protection against infectious material entering the brain is only the thin tissue of the olfactory mucosa. In a later discussion, under the heading of polypharmacy, details on a source of damage reducing protection against infectious material entering the olfactory bulb is presented. We have, at hand, vaccinations and antibiotics known to be effective in curbing infections and their use should surely be used in the service of reducing the risk of Alz.

The Commission ended their summary with this conclusion: "Modifying 12 risk factors might prevent or delay up to 40% of dementias" (p 3). The full report of the Commission provides full documentation of findings germane to the report and reflects a massive amount of work.

Polypharmacy is a multi-faceted risk germane to developing dementia.

The Lancet Commission failed to mention **polypharmacy** as a significant risk for developing Alz. The consensus: taking 5 or more drugs concurrently is risky. It is likely that the combined side-effects of taking multiple drugs concurrently can produce mild to severe disease which may be treated by the prescription of another drug. Ethanol and nicotine are often not counted when tabulating number of drugs being taking.

The American Geriatric Association has about every 3 years published a list of drugs that are *Potentially Inappropriate Medications* (PIMs) in consideration of the older citizenry. The publications are named after a first of such publications by a physician named Beers, hence named the Beers' Reports or Beers criteria. Recent lists of PIMs are compiled by experts on pharmacology. There are, surprisingly, approximately 100 drugs, that should be avoided. However, that list does not include all the brands used to market the PIMs. Although compiled to protect the elderly, I see no reason why it is not also a guide for prescribing for all ages. Yes, the elderly has effects of the weathering of aging weakening such as their immune systems, and bodily organs; however, given that there are often alternatives to the PIMs, it just seems prudent to not recommend medications (with very few exceptions) of any of the list of drugs the Beers Report deemed potentially inappropriate and should be avoided.

Among the drugs the Beers Report indicated should be avoided are many drugs authorized for prescription by agencies such as the Food and Drug Administration of the USA for depression, a variety of anxiety disorders, and schizophrenia. However, these same drugs can be prescribed by physicians for other problems. These unwholesome drugs are used to quell "misbehavior" among young children (e.g., Reebye & Elbe, 2009). Also, powerful antipsychotic drugs have been used to control elderly patients without regard for the functions of the dopaminergic systems of the brain among which is positive affect (e.g., Ray et al., 1980).

Various laboratories have assessed the anticholinergic effects (called anticholinergic burden) of many commonly used drugs. Many drugs have anticholinergic effects, hence interfere with physiology involving cholinergic neurons and receptors. The norm is for drugs to be classed as having a severe anticholinergic burden (labelled 3), a moderate burden (labelled 2) or a mild burden (labelled 1). The theory is that the burden of one drug can add with a burden of another drug to yield an overall burden score, e.g., a drug with a burden of 3 accompanied by a drug with a burden of 2 will yield a burden of 5. Now it is clear that the numbers do not necessarily fall on equal intervals allowing the scores to be added; however, there is a consensus that drugs with anticholinergic burdens given concurrently have more effects than each alone.

The label anticholinergic *burden* is germane in as much as a drug with an anticholinergic burden interferes with the functioning of the cholinergic systems are which are widespread throughout the physiology, e.g., acetylcholine is the neurotransmitter at neural-muscular junctions, acetylcholine is involve in the regulation of major organs of the trunk, and acetycholinergic neurons are involved with various circuits of the brain. The extent of the burden is dose-related and there is a consensus that a burden of greater than 4 or 5 induced by drugs and drugs' side-effects when taken concurrently is indeed a burden.

Patrick Angerame, a student working in our Alzheimer's Prevention Project, has listed 23 generic drugs all approved by the FDA of the USA but with a severe anticholinergic burden (rated 3). These generics have associated with them 203 brands. Any two of these brands signals a considerable risk of disease. There are more drugs with a burden score of 2 and 1. Many of these drugs are listed in the Beers Report. Given the fact that many elderly citizens are currently taking more than 5 drugs daily provides a strong possibility that the combined effects of multiple drugs are likely to induce a severe anticholinergic burden, which, in turn is disruptive of homeostasis of multiple systems of a physiology sustaining health and well-being.

Given the well-known involvement of the cholinergic systems of the brain and spinal cord to the regulation of organs of the trunk, the muscular system and brain-functioning, failure to manage the use of drugs with known severe anticholinergic burdens seems contrary to the credo "do no harm."

Toxicity associated with the use of drugs that dry the respiratory mucosa.

The entire airway from nostrils to the depths of the lungs is lined with the respiratory mucosa which includes its innate immune system. The system is very efficient, e.g., curing the common cold among youngsters and others, yearly, and often a few times a year, usually in less than 10 days. The innate immune system of the airway achieves its efficiency by the secretion of mucus, a watery, viscous, very sticky substance. The mucus is exposed to all incoming and outgoing air. The turbulence generated by constant intake and outtake of air about the bones the of nasal cavity exposes the contents of the incoming air to the sticky mucous hence "capturing" microbes and particulate matter that might be in the inhaled air.

Beneath the airway's mucus is a layer of serous fluid. Beneath the layer of serous fluid is a line of epithelial cells. The epithelial cells have cilia extending into the serous fluid. The cilia, via circular brush strokes, move the mucus layer (at a speed of 2 to 25 mm/min depending on degree of contamination, faster with more contamination, along with its captured microbes and dirt to the back of the throat. The contents are then regularly swallowed dumping the mucus and its captured contents into the stomach's acid (the process is rightfully called mucociliary clearance). Also, an accumulation of contamination of microbes and

dirt often engenders sneezing, a runny nose, coughing, and hacking up gunk, all in the service of clearing the airway and protecting the lungs from being infected.

The innate immune system of the airway can be overwhelmed by excesses of dirt and microbes, hence reducing its efficiency, and putting at risk the lungs due to microbes reaching the alveoli of the lungs where they might multiply engendering pneumonia. Although not as obvious as risks to the lungs, there is a risk to the brain as well.

Only a thin layer of the olfactory mucosa overlays the many foramina of the cribriform plate. The mucosa's epithelial cells are the physical barrier protecting microbes from entering the foramina. The foramina are pathways through the skull for filia of the olfactory nerves and are known to allow viruses to invade the olfactory bulb (Itzhaki et al., 2016). Due to a slow movement of the mucus layer of the innate immune system, viruses might accumulate at epithelial cells guarding the openings in the skull. A prolonged viral load risks a viral infection of epithelial cells which eventually kills the cells hence breaking the only physical barrier and allowing viruses to ascend into the olfactory bulb (Dasaraju & Liu, 1996).

When viruses or other debris might invade the olfactory bulb, the immune system of the brain will be engaged in clearing the viruses and any dying cells. When there is a failure of the immune system to clear the viruses and infected cells of the bulb, more functionalities of the immune system are employed which can include such as a flood of cytokines. Cytokines can kill healthy cells, hence generating more debris to be cleared. Further enlistment of immune cells and cytokines might lead to inflammation which, in turn, kills more healthy cells. The consequences might lead to a slow progression of attacks on adjacent healthy cells setting a slow, but insidious march of neuronal death toward other areas of the brain including the hippocampus.

A buildup of contamination within the outer layers of the airway is sensed via special sensory cells (Hariri & Cohen, 2016).), which in turn sets in motion preventive events, including release of antibacterial secretions, and increased speed of mucociliary clearance. The serous fluid needs to be replenished constantly but more so with faster mucociliary clearance. The increase of fluid due to vasodilation can cause a swelling of the respiratory mucosa. That influx of fluid is often manifest as a feeling of congestion, a runny nose, coughing, lethargy and bad feelings. Such can be perceived as symptoms of disease, e.g., likely a common cold or maybe flu or other diseases, which are activating the actions of the innate immune system. Those manifestations of uncomfortable symptoms are the actions of the innate immune system in the service of protecting lungs and brain from insults. Note, a dry mucus does not capture microbes or dirt. A depleted serous fluid does not move mucus and captured contaminants out of the airway, hence allowing infectious material to descend into the lungs. A dry mucus allows viruses to multiple and linger among the cells of the olfactory mucosa hence increasing the risks of infection merely one step away from the olfactory bulbs (Reid et al. 2020).

The preceding paragraphs were written to make an obvious point. One should not do anything interfering with the innate immune system of the respiratory airway. However, millions of citizens unwittingly do interfere with functionality of the immune system when they take drugs drying the respiratory airway. Widely advertised and skillfully marketed retail drugs produce the drying of the airway in the service of not being uncomfortable with the "symptoms" of the common cold and allergies. Many retail drugs advertised as a remedy for insomnia also tend to induce dryness of the respiratory mucosa because they generally have similar ingredients as the so-called meds for "cold and flu" (such is a label on containers displayed on retail stores shelves and of course do not cure the flu). The drugs, e.g., antihistamines, constrict the blood vessels suppling the extra fluid needed for efficient mucociliary clearance. Often these drugs also have a severe anticholinergic burden.

The drugs sold in retails stores for the common cold and insomnia do not cure or shorten the presenting disease, they merely reduce symptoms manifest *by the curing activity* of the innate immune system of the respiratory mucosa (Sutter et al., 2012; Sutter et al., 2015; Duncan-Lewis, et al., 2011). For sure, these cold and insomnia "meds" will not protect, the lungs and brain from emerging viral infections, e.g., the viruses of COVID-19.

Typically, cold viruses do not induce fever. However, flu viruses and viruses of COVID-19 do induce fever. Consequently, we have an index of when more than a retail-store-medicine should be used. However, some of the cold meds also have as an ingredient acetaminophen (common brand name, Tylenol). Tylenol is an effective drug for reduction of pain and fever. Note, Tylenol masks a cardinal symptom, i.e., fever, associated with deadly infections which call for nearly immediate, expert medical attention.

Unfortunately, polypharmacy is a serious risk-factor for the development of Alz if for no other reason many sold drugs have a severe anticholinergic burden. Also, many drugs do have harsh side-effects adding to the chaos caused by other drugs. The remedies for harshness of polypharmacy are clear, i.e., better management and regulations of the drug-trade.

CONCLUSIONS

Any citizen not getting a sufficient, nearly daily supply of B-vitamins by ingesting food (manifest by Hhcy) and concurrently taking two or more drugs with a severe anticholinergic burden is likely to have induced chaos in the citizen's physiology. Such is due to the basic facts that diminishing the processing utilizing B-vitamins and acetylcholine are critical (yes essential) to many facets of a healthy physiology. If that citizen usually has an alcoholic beverage with lunch and dinner, the citizen is potentially creating Hhcy due to ethanol's interference with the transfer of vitamins from food to the circulation. If that same citizen has trouble getting a good night's sleep and then takes a sleeping pill, perhaps even nightly, there will be even more disruption of homeostasis and more chaos. If the citizen is elderly and the weathering of aging has weakened an organ, the physiological chaos is likely to be manifest first in a vulnerable organ system. A well-meaning health-care professional is, therefore, apt to treat the manifestation of the suspect disease with another drug, hence increasing the risks associated with polypharmacy. If this same citizen gets a common cold and takes a cold "medicine" designed to dry the innate immune system of the airway, that citizen is at risk for infections of lungs and brain. All circumstances related above are dose-related and excess of any one of the drugs or circumstances is apt to be a setting condition for such as cardio-vascular diseases which are also risks for Alz. In brief, it is an accumulation of the effects of risk-factors some listed above that contributes to an acceleration of aging leading to losing a mind, becoming helpless and then dying younger than necessary.

Aging itself not *the* cause of Alz, but enhancements of the weathering of aging can induce circumstances leading to a breach in the various systems nurturing and protecting the brain. For examples, but not a full list, of enhancements of the weathering of aging of the brain are such as clogged arteries due to a poor diet featuring LDL lipoproteins, poor diets not suppling sufficient nutrients such as the B-vitamins and choline, weak hearts and other muscles due to insufficient exercise, poor choices of supposedly helpful drugs manifest by many brands of drugs with a severe anticholinergic burden, insufficient attention to the risks imposed by taking many drugs concurrently, insufficient vaccinations, and air pollution including deliberately inhaling addictive drugs.

The scientific community tends to ignore the pervasive effects of commercial interests which not only governs much of what we ingest and breathe but what we believe. The one circumstance hardly mentioned in theories of cause of Alz (and other diseases) is the influence of the commercial culture. For example, the sale of drugs for the common cold, which are basically not particularly helpful, but risky nevertheless. The risk of excess inhaling the smoke of burning tobacco and marijuana plants and intake of alcoholic beverages are risk of developing Alz and other diseases but are successfully promoted and those ads and public relations are extraordinarily effective because they are based on the science of behavioral manipulation. The sale of tobacco products, alcoholic beverages and cold & allergy meds yield huge profits and hence are perpetuated despite knowing the harm they can induce. Commercial interests are clearly inherent to pharmaceutical companies and suppliers of tools for scientific research, but also the financial interests of "owners" of scientific journals, and the managers of not-for-profit associations (includes universities, professional organizations, and charities) while paying executives considerably more money than paid to executives of many successful for-profit businesses. *There are marvelous benefits via competitive commercial enterprises;* however, companies and not-for

profit organizations must be regulated so that health and welfare is not harmed. Further efficient regulation ultimately benefits commercial enterprises. Some cultures condone citizens making money nearly anyway they can which is often in conflict with the aim to make money by being useful, helpful, and providing goods and services sustaining health and happiness. Regulations favoring the latter and discouraging the former can reduce diseases.

To prevent Alz, individuals and communities can engage biologically and sociologically informed cognitive behavioral technologies to avoid accelerating the weathering of aging. The sociologically informed involves a consideration of the influences of commercial enterprises which are pervasive and often not well-regulated. The prevention of Alz involves stopping engagement in toxic activities, e.g., prescribing benzodiazepines for treating insomnia and some forms of anxiety, which are now known enhances all causes of diseases, an obvious enhancement of acceleration of aging (Kripke, 2016b). Polypharmacy can be reformed sufficiently to curb disease, e.g., by avoiding drugs with an anticholinergic burden and attending to the Beers Report. There are activities such as adequate nutrition and vaccinations which aid and abet health, hence does not accelerate aging. The conceptualization, the approach, that Alz is a function of the degree of enhancements of aging (although rather obvious) focuses on multiple potential remedies, rather than a single cause of Alz (an idea that has seemingly failed and failed often). Studies focusing on the rate of weathering of aging and ways to repair or stop some obvious causes accelerating aging is likely to reduce premature onset of loss of cognition and early death. Further, the rate of accelerating aging can be indexed by rate of cognitive decline which is rather easy to measure and will be useful in doing research on causes of acceleration of aging.
The Lance Commission posited that their 12 risk factors, if attended to, would have reduced about 40% of the current prevalence of advanced Alz and other causes of dementia and do that in the future as well. If there were more intense interventions to limit the risk of their 12 identified risks plus other risks such as chronic insomnia, excessive polypharmacy with more prudent limits on identified PIMs, more attention to nutrition so that such as Hhcy does do not emerge and further attention to the possibility of infections reaching the brain, we could surely, significantly not accelerate the rate of the weathering of aging. In so doing, reduce the rate of development of Alz and protect the integrity of the brain. Further, we have proven ways of accomplishing a reduction of salient risks.

Attending to nutritional deficiencies (e.g. B-vitamin & choline) and avoiding deleterious drugs are within our grasp, but not dealt with efficiently. Other risks accelerating the weathering of aging can be altered for the better often by such simple measures as buying an air filter or taking daily walks. There are Cognitive behavioral technologies proven to help citizens engage in overcoming chronic insomnia, anxiety disorders, depression, & stress and they should be standard interventions rather than relying on drugs with, at best, marginal efficacy, and long-term harms. Excessive polypharmacy will surely accelerate the weathering of aging.

Older citizens can by their own behavior can set their physiology to, in turn, set the conditions for preventing late-onset Alzheimer's disease. Further, older citizens should know if a drug is discovered that can apparently “cure” Alz is on the horizon, the drug would not likely be widely available during the last decades of their lives. A first step toward avoiding the development of Alz (not accelerating aging) is to vigorously promote that Alz, and related diseases, can be prevented via citizens own activities. If citizens are having difficulties engaging preventive actions, they should know that expert advice and help is available often at little cost.

The recognition that better behavior induces better physiology and better physiology stands a good chance of preventing disease does not seem to be the prevailing conceptualization guiding the management of Alz and related diseases.

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