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Dementia – What is its Causal Etiology?

Commentary

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Since Antiquity, medical texts have referred to dementia (see the writings of Pythagoras, Solon, Plato, Cicero, Celsius, Galen, Bacon,... and others in Asia and China). Until the end of the 19th century, it was a much broader clinical concept that encompassed mental illness and any type of psychosocial incapacity. It was uncommon in pre-industrial times and relatively rare before the 20th century. In the elderly, it was believed to be the result of blockages of the major arteries supplying the brain or small strokes within the vessels of the cerebral cortex (two forms of cerebral atherosclerosis). It was only recently, on the basis of symptomatology, pathological examination of brain tissues, and different patterns of brain metabolic activity that a number of other types of dementia have been identified. However, the causal etiology of many types of dementia, including Alzheimer's disease, still remains unclear and many theories (rather hypotheses) have been advanced, but these are largely based on risk factors, associations or correlations. More recently, I have posited that the *root cause* of Alzheimer's and other neurodegenerative diseases may be a runaway autoimmune disease.

With increasing lifespan in the developed world, dementia has emerged as an increasing public health concern. As more people are living longer, dementia is becoming more common in the population as a whole due to a decrease in risk factors. *Global Health Estimates 2016* lists Alzheimer's and other dementias as fifth among the top 10 global causes of mortality. It costs annually $818 billion excluding the majority of care that is provided by partners or/and family careers.

Most dementia types are slow and progressive. Symptoms vary across types and stages and also with the individual. A diagnosis requires a change from a person's usual mental functioning and a greater decline than one would expect due to aging. The disease also has a significant effect on a person's caregivers. The signs and symptoms evolve in three consecutive phases (early, middle, and late phase) ending up in near total dependence and inactivity, serious memory disturbances, and more obvious physical signs and symptoms. Behavioral and psychological symptoms of dementia occur almost always in all types of dementia and may manifest as agitation, aggression, anxiety, apathy, appetite changes, behavioral changes, delusions/hallucinations, depression, disinhibition, impulsivity, irritability, mood elations, motor abnormalities, psychosis, and sleep disturbances.

Each form of dementia has its own risk factors, but most forms have several risk factors in common. These are age (the biggest risk factor), family history, and other factors including lifestyle, high blood pressure, smoking, and diabetes. It is not known how treatment for these problems influences the risk of developing dementia. It seems as though people who remain physically active, socially connected, and mentally engaged are less likely to fall prey to dementia (or develop dementia later) than others. To compound things, more than one type of dementia may exist in the same person.

Symptoms are very similar in all types of dementia and thus cannot by themselves help in reaching the correct diagnosis of demential type(s). At present, the main contributors to dementia are Alzheimer's disease dementia (50-70% of cases), vascular disease dementia (25%), Lewy body dementias (15%), others of unspecified contribution including Parkinson's disease dementia, frontotemporal disorders dementia, and still others (mixed, senilitic, syphilitic, progressive supranuclear palsy, corticobasal degeneration, encephalopathy, and Creutzfeldt-Jacobs disease dementia). Immunologically mediated, chronic inflammatory conditions include Behcet's disease, multiple sclerosis, sarcoidosis, Sjogren's syndrome, systemic lupus errhythematosus, and celiac and non-celiac diseases. There are still many other medical and neurological conditions in which dementia only occurs late in the illness.

Inherited conditions include various diseases (Alexandre's, Krabbe's, Niemann-Pick type C, maple syrup urine, Pelizaeus-Merzbacher), syndromes (fragile X-associated tremor/ataxia, San Filippo type B), epilepsy, and many other disorders (cerebrotendinous xanthomatosis, dentatorubal pallidoluysian atrophy, fatal familial insomnia, glutaric aciduria type 1, neuronal ceroid lipofuscinosis, neuroacanthocytosis, organic acidemias, spinocerebellar ataxia type 2, and urea cycle).

There are, nonetheless, some reversible conditions such as hypothyroidism, Vitamin B_{12} deficiency, Lyme disease, and neurosyphilis. All people with memory difficulty should be checked for hypothyroidism and B_{12} deficiency. For Lyme disease and neurosyphilis, testing should be done if there are risk factors for those diseases. Because risk factors are often difficult to determine, testing for psychoneurosis and Lyme disease, as well as other unmentioned factors, may be undertaken as a matter of course in cases where dementia is suspected.

Except for the treatable types of dementia listed above, and in the absence of a thorough understanding of the deep biology of this disease, there is currently no cure. Medical interventions remain heretofore palliative in nature with aim to alleviate pain and suffering.

In my book "*Dementia: Fending off the menacing disease and what you can do about it*", I set forth what can be done about it, in addition to seeking available medical treatment. After defining dementia, its symptoms and effects, the areas of the brain and the functions affected, and their deleterious sequelae, I explained why dementia remains one of the most misunderstood disease in contemporary medicine. I described in general terms the various disorders and factors that contribute to the development of dementia with correspondingly diverse symptoms. I also classified them according to three broad categories, namely, the affected brain area (including cortical and subcortical dementia), the progressiveness and irreversibility of the disease (the case of Alzheimer's, vascular, Lewy body, frontotemporal, and mixed dementia), and the derivability from another primary disorder (such as Alzheimer's disease) or secondary disorder (including brain infections, progressive supranuclear palsy, and multiple sclerosis). I discussed the many other conditions that cause dementia-like symptoms but can be halted or even reversed with treatment. These include alcoholism, necrophiliac brain disease, children's dementia, chronic traumatic encephalopathy, Creutzfeldt-Jakob disease, HIV-associated dementia, Huntington's disease, immunologically-mediated dementia, inherited conditions, progressive supranuclear palsy, traumatic brain injury, and others. Dementia-like conditions that can be reversed with treatment include anoxia, b**rain tumors, drug reactions, infections and immune disorders, metabolic problems and endocrine abnormalities, normal-pressure hydrocephalus, nutritional deficiencies, poisoning, and subdural anathemas.** Several conditions that can cause serious memory problems that resemble dementia should go away once the conditions are properly diagnosed and treated. These include emotional problems, injuries (particularly head injuries), medical conditions (blood clots, brain infections, kidney problems, liver problems, thyroid problems, tumors), and several other conditions such as alcoholism, medicines' side effects, and vitamins (B_{12}) deficiencies.

I elaborated upon the signs, symptoms and stages of dementia. Signs and symptoms result when once-healthy neurons (nerve cells) in the brain stop working, lose connections with other brain cells, and die. Everyone loses some neurons as they age, but people with dementia experience far greater loss. The stages of dementia are loosely grouped into mild, moderate, and severe categories. Other staging's have also been adopted. However, the different stages of dementia cannot be used to predict how rapidly someone's condition might progress and patients may remain in one stage for many years or for only a few months. Every patient has a different disease progression. Nonetheless, stage diagnosis can help create a personalized treatment plan.

I addressed the causes and risk factors of dementia. All forms of dementia are the end result of either cell degeneration and death or abnormalities, impeding communications between brain cells (neurons). Depending on the area of the brain that is affected by the damage, dementia can affect people differently and cause different symptoms. In many of the common types of dementia, abnormal proteins (or abnormal amounts of normally-occurring proteins) are found in the brain tissue at the microscopic level. However, it is not known if these proteins cause dementia or if they result from the disease themselves. While some types of dementia are hereditary, many are a result of a combination of genetics, environment, and lifestyle (my acronym **GEL** for this guilty triad!). I identified the several risk factors for developing some types of dementia and suggested ways to minimize them.

Because the symptoms of various dementias can make it hard to get an accurate diagnosis and because the different diseases are treated differently, it is important to be able to make the correct diagnosis. Indeed, a correct diagnosis is a prerequisite to get the right treatment. I therefore discussed the various ways available for screening and eventually diagnosing dementia together with a review of the principal tests available.

I also discussed in great detail the various important types of dementia: Alzheimer's, vascular, Lewy body, frontotemporal, and Parkinson's. For even more details on Alzheimer's and Parkinson's, I refer the interested reader to my previous books on these subjects. People often wonder about the difference between any of these diseases and the corresponding dementia. The disease (for example, Alzheimer's) is but a symptom of the dementia (Alzheimer's disease dementia). A number of hallmarks have been identified for each such disease, however, these are only hallmarks, *not* causes. Whereas they are still considered the main disease features, many other complex brain changes are thought to also play a role. Additionally, I discussed the gold standard for Alzheimer's diagnosis and its staging whether functional or/and cognitive. Using whole-genome sequencing and whole-exome sequencing, new genes have been identified that contribute to or protect against disease risk (again, we are speaking of protection against a risk factor, not elucidating the root cause of the disease). An environment (free in as much as possible of toxicities, harmful electromagnetic radiations, and other physical and chemical factors) and a healthy lifestyle (nutritious *d*iet, physical activity and *e*xercise, *s*tress reduction, restful *s*leep, *s*ocial engagement, and *s*timulation of mental pursuits,... my acronym **DES4**) may help people stay healthy as they age. Clinical trials have indeed begun testing some of these possibilities.

The second most common type of dementia, vascular dementia was considered. It refers to the progressive loss of memory and other cognitive functions caused by vascular injury (strokes, atherosclerosis, endocarditis, or amyloidosis) or structural damage to the brain tissue (either by blocked arteries, blood clots, or hemorrhage). Its symptoms may sometimes be difficult to distinguish from Alzheimer's disease, *albeit* memory loss is more prominent in Alzheimer's. People with dementia seldom have only Alzheimer's-related changes in their brains. Any number of vascular issues may also be at play. The six types of vascular cognitive and impairment disorders were reviewed, including multi-infarct dementia, post-stroke dementia, vascular cognitive impairment, cerebral autosomal-dominant arteriole with subcortical infarcts and electroencephalography, and subcortical vascular dementia (aka Harbinger's disease).

I treated Lewy body dementias that encompass all dementias whose primary cause is Lewy bodies in the brain. **It is a complex** progressive neurodegenerative disease wherein abnormal deposits of the alpha-synucleic protein (what are called "Lewy bodies") build up in multiple areas of the brain that regulate behavior and mood, cognition, and movement. **Because its symptoms can closely resemble other more commonly known diseases like Alzheimer's and Parkinson's, it is currently widely under-diagnosed. However, d**ementia with Lewy bodies is not a rare disorder. Typically, it begins after the age of 50 or older, although sometimes younger people have it. It can be challenging to diagnose, and many primary care physicians are not trained to recognize it or distinguish it from Alzheimer's disease dementia. I discussed the several available diagnostic, laboratory and screen tests,

and other well-developed questionnaires, and biomarkers that are employed to arrive at either a *probable* or a *possible* diagnosis. Part of the challenge in diagnosing dementia with Lewy bodies is that the patients with the disorder often present with different constellations of symptoms. In addition, there are no standard procedures for health providers to use in applying the consensus diagnostic criteria in daily practice.

I further discussed frontotemporal disorders that are the result of damage to neurons (nerve cells) in parts of the brain called the frontal and temporal lobes. As neurons die, the lobes atrophy (shrink), gradually causing difficulties in cognition and behavior. Many possible symptoms can result relating to behavior, communication, emotions, or movement. In most cases, the cause of the disorders is unknown. Individuals with a family history are more likely to develop such disorders. People can live with frontotemporal disorders for up to 10 years, sometimes longer, but it is difficult to predict the time course for any individual patient. In the early stages, people may have just one type of symptom. As the disease progresses, other types of symptoms appear as more parts of the brain are affected. No cure or treatments that slow or stop the progression of the disorders are available today. However, research is improving awareness and understanding of these challenging conditions, opening doors to better diagnosis, improved care, and eventually new treatments.

Parkinson's disease, a long-term degenerative disorder of the central nervous system, was dwelt upon. The disease belongs to a group of conditions called motor system (or movement) disorders. It is both chronic (that is, it persists over a long period of time) and progressive (its symptoms grow worse over time). It is a common, disabling, and currently an incurable neurodegenerative condition. It results from the loss of dopamine-producing brain cells in a deep region of the brain called the *substantia nigra*. It is the second most common neurological disorder after Alzheimer's disease. The symptoms appear in four different categories: primary motor symptoms, non-motor symptoms, neuropsychiatric symptoms, and alterations in the autonomous nervous system. The causes are generally unknown, some cases are hereditary and can be traced to specific genetic mutations, others do not typically run in families. Since there currently are no blood or laboratory tests, the diagnosis is mainly based on symptoms with imaging scans (CT, MRI, PET, and SPECT). Available treatment options include drug therapy and surgery (intentional lesioning, pallidotomy, and thalamotomy). Initial treatment is typically with the drug *Levodopa* and dopamine agonists are used once the drug becomes less effective. Diet and some forms of rehabilitation have shown some effectiveness at improving symptoms. Various forms of Parkinson's result from neurological disorders. The life expectancy of people with Parkinson's disease is reduced. Parkinson's disease dementia starts as a movement disorder with symptoms consistent with a diagnosis of Parkinson's disease. As the years progress, patients may develop cognitive symptoms, which result in difficulty with daily functions. In managing and treating Parkinson's disease dementia, antipsychotic medications are avoided given the high likelihood of a negative reaction.

Many neurodegenerative conditions that share cognitive and motor symptoms were studied. The differential diagnosis is between the various types of dementia: Alzheimer's, vascular disease, multi-infarct, Lewy bodies, frontotemporal disorders, and Parkinson's. To these are grafted several Parkinson-related conditions. Preliminary differentiation could be achieved through a comparison of the signs and symptoms of the respective dementia types. However, s**ymptoms may not always tell the whole story!** Several neurodegenerative disorders may also present with Parkinson's; they are sometimes referred to as "atypical Parkinson" or "Parkinson+plus syndromes", that is, Parkinson plus some other features distinguishing them from Parkinson's disease. They include multiple system atrophy, progressive supranuclear palsy, corticobasal degeneration syndrome, dementia with Lewy bodies, and psychopathy.

Assembling and succinctly summarizing much of the known information on dementias with regard to the issues of their common or respective assessment, management, treatment, and prognosis can provide a better overall appreciation and understanding of these several dementia types. Unfortunately, there is no cure for any type of dementia; however, in the case of Alzheimer's, early brain changes point to a possible window of opportunity to prevent or delay debilitating memory loss and the later symptoms of dementia. For multi-infarct dementia, medication and cognitive training can help preserve mental function. For dementia with Lewy bodies, fortunately, some symptoms may respond to treatment for a period of time. Beyond medications, managing the disease may involve physical and other types of therapy, and counseling. For Parkinson's, there is likewise no cure but medications, surgery, and physical treatment can provide relief and are much more effective than treatments available for other neurological disorders. Many patients may benefit from combination treatments. Current non-pharmacological treatment approaches focus on helping people maintain mental function, manage behavioral symptoms, and slow down certain problems, such as memory loss. Researchers hope to develop therapies targeting specific genetic, molecular, and cellular mechanisms so that the actual underlying cause of the disease can be stopped or prevented. There is no standard drug treatment for vascular disease dementia. Treatment of multi-infarct dementia focuses on controlling the symptoms and reducing the risk of future strokes. Being a multi-system disease, dementia with Lewy bodies typically requires a comprehensive treatment approach. Only palliative care can now be offered. However, medications are one of the most controversial subjects in dealing with the disease. Extreme caution is required in the use of antipsychotic medication because patients who take neuroleptics are at risk for neuroleptic malignant syndrome, a life-threatening illness.

I also reviewed the wide variety of existing complementary and supportive therapies. Given the progressive and terminal nature of dementia, palliative (comfort) care can help manage symptoms and has a role in improving a person's quality of life by relieving disease symptoms. It is recommended before the late stages of dementia. It also helps caregivers in understanding what to expect, dealing with loss of physical and mental abilities, planning out a patient's wishes and goals including surrogate decision making, and discussing wishes for or against cardiopulmonary resuscitation and life support. Lastly, I addressed many of the challenges of caring for someone with moderate or advanced dementia, covering several topics: support network, patient's basic care, financial and medical matters, safety of the patient's environment, resources available to the career, lifestyle changes, and the patient's ability to continue to drive.

Can dementia be prevented is a topic I attacked head on. While there is no way to absolutely prevent the development of dementia, different activities have been identified which might decrease the risk. Unfortunately, there is no evidence of benefit to delay or prevent age-related cognitive decline, mild cognitive impairment or Alzheimer's dementia. However, there is encouraging although inconclusive evidence for three specific types of interventions: **Cognitive training; blood pressure management for people with hypertension; and increased physical activity.** Pending a better understanding of the root cause of Alzheimer's disease dementia, preventing it begins by minimizing or hopefully eliminating its several symptoms. In addition, despite observational studies that link Mediterranean- (and Japanese-) style and other diets to brain health, clinical trials have not so far shown strong evidence. However, many of these trials have focused on individual foods rather than comprehensive diets so their results should not be taken at face value. There is not enough evidence to recommend exercise as a way to prevent Alzheimer's dementia or mild

cognitive impairment. There is much variability in the link between stress and illness as stress is often associated with much higher risks of cardiovascular disease because of the compromised immune system. Common sleep problems are associated with increases in some biomarkers of Alzheimer's. The right quantity and quality of sleep need to be emphasized. Mental and physical exercises have similar benefits in lowering the risk of Alzheimer's and slowing the rate of cognitive decline in older adults. Social isolation and loneliness are related to health problems such as cognitive decline, depression, and heart disease. Fortunately, there are ways to counteract these negative effects by engaging in meaningful, productive activities with others. Social integration is a powerful predictor of health and longevity. However, more controlled, longitudinal experiments need to be carried out for confirmation.

Beyond seeking available medical treatment, there are several national and private organizations that offer invaluable services. Even though dementia cannot be stopped or reversed, beginning treatment early in the process may help preserve daily functioning for some time. An early diagnosis also helps families plan for the future. At this time, whereas dementia is generally not reversible, there are things that can be done for coping and living with dementia. What foods one eats, how much physical activity one chooses to participate in, how mentally active one is... all affect one's state of health - both physical and cognitive. Much research has been conducted on these lifestyle choices and the conclusions have repeatedly shown that they can all play a role in cognitive functioning. Additionally, quality of life is possible, despite the diagnosis. This often involves social interaction with friends and opportunities for meaningful activities. There are many ways to plan ahead, but it is important to focus on living with dementia and finding enjoyment every day despite the many challenges and adjustments needed. Further, planning for the end of life can be a valuable activity for any family. There are several consumer web sites about hospice and palliative care managed with state-specific advanced directives. There are also several advocating and supporting organizations that offer valuable help.

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None.

Conflicts of interest

The author declares that there is no conflicts of interest.

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