

The Impending Alzheimer's Disease Pandemic

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An epidemic occurs when a disease propagates uncontrollably within a population over some defined period of time. If the spread becomes worldwide, then the epidemic becomes a pandemic. Traditionally, epidemics have arisen from the rapid spread of an infectious disease, such as smallpox, plague, cholera, typhus, or malaria. For centuries, these pathogens wrought havoc on ill-equipped and ill-prepared populations. This year bears a potent reminder of the danger, as it marks the 100th anniversary of the 1918 Spanish Flu influenza epidemic, one of the most lethal diseases in human history which killed 50 million people.¹

However, as society changes, so will the causes of our future epidemics and pandemics. One looming threat, and one for which we are woefully underprepared, is Alzheimer's disease (AD): an age-related disorder that causes progressive, and ultimately fatal, degenerative dementia. As lifespans increase around the world, and the massive baby-boomer generation approaches old-age, AD has begun to spread rapidly. At present, there are 7.7 million new cases per year worldwide – that's a new case of AD every four seconds.² The number of people with AD is projected to rise by 55% by 2030, and by 2050 more than 135.5 million people will be struggling with, and ultimately dying from, AD.³ The spectre and spectrum of AD, combined with its health and socioeconomic impact, has the capacity to affect every population in the world.

In Canada, some 750,000 Canadians suffer from this mind-robbing condition that impairs memory, thinking, and behaviour, and one new person joins them every five minutes.^{3,4} It is estimated that by 2030, this number will have nearly doubled to 1.4 million.⁴ Considering that AD is already the seventh leading cause of death worldwide, the impending toll, as the pandemic fully manifests, may become catastrophic.⁵

There are no disease-modifying or curative agents for AD.⁶ The design, development, and optimization of a pioneering disease-modifying drug is a neuropharmacological priority. However, halting the full impact of the impending AD pandemic is undoubtedly going to take more than a drug. Alzheimer's is a disease that devastates not only individuals but also families, societies, and nations. Accordingly, addressing this epidemic requires a multi-pronged attack targeting all aspects of the disease – from molecules to cells, from individual lives to their families and societies. To achieve this goal, we need to better understand all the varied aspects of AD.

Our molecular level understanding of AD is still evolving. In 2018, there are two dominant hypotheses concerning the cause of AD: the proteopathy hypothesis and the immunopathy hypothesis. The proteopathy hypothesis proposes that proteins such as beta-amyloid or tau misfold and become

oligomerized or clumped. These species become toxic to the brain, destroying neurons and eventually causing AD to progress.⁷ The immunopathy hypothesis proposes that immune cells in the brain called microglia become overactive in AD. These activated microglia then elicit the expression of pro-inflammatory cytokines such as interleukin (IL)-1 β , IL-6, and tumor necrosis factor- α (TNF- α), influencing the surrounding brain tissue and damaging neurons, thus causing AD to progress.^{8,9} Over the past 20 years, most research has focussed on proteopathy, whereas the immunopathy hypothesis has only recently garnered attention. However, it must be remembered that 40-50 years ago, researchers felt that aluminum exposure might be the cause of AD – a hypothesis that did not stand the test of time.¹⁰ The eventual success or failure of the proteopathy and immunopathy hypotheses must therefore await experimental validation.

At the cellular and tissue level, AD is characterized by the death of neurons and the activation of glial cells. A normal adult human brain weighs 1300-1400 g; a person who has succumbed to AD will have a brain weighing less than 900 g.¹¹ The thick grey cortical mantle of cells that envelop and embrace the brain will be especially devastated.¹² Neuronal support cells are also involved, as immunotoxic microglial activation contributes to disease progression.⁹ Ultimately, plaques (aggregates of beta-amyloid) and tangles (aggregates of tau) will become the tombstones of dead neurons as the brain irreversibly degenerates.

At the level of the individual, AD is truly devastating. Alzheimer's slowly destroys memory, thinking, and eventually all ability to function. The disease erases personality and makes even routine tasks like dressing and bathing impossible. The afflicted individual is unable to recognize their spouse of fifty years and is incapable of identifying their own children. More than cancer, more than heart disease or lung disease – for seniors, dementia is the single greatest cause of disability and debilitation. Its cruel course robs people of what they treasure most: memories, skills, relationships, independence – and then the body starts to wither and waste.

AD can also be overwhelming for the families of affected people and for their caregivers. Parents with dementia are often moved into family homes, causing domestic stress. Children often give up their jobs to care for their dementing parents, causing additional strains within a family unit. Moreover, it is being increasingly recognized that AD and domestic abuse are not independent processes. Up to 60% of people with dementia abuse their caregivers in some way and 12-55% of people with dementia are physically abused by their caregivers – a worrisome observation given the increased suscep-

tibility of the frail and elderly to bodily harm.^{13,14} This dementia-domestic abuse correlation is not a simple cause-and-effect relationship but rather a complex, underappreciated (or perhaps simply ignored) medical-societal synergy.

Alzheimer's is not only a profound human tragedy but imposes an overwhelming economic cost as well. Dementia has significant socioeconomic implications in terms of direct medical, social, and informal care costs. Due to the length of time people live with and need care for the illness, it's among the most expensive medical conditions in the world and may soon become the most costly disease in human history.¹⁵ Dealing with dementia already costs Canadians \$15 billion a year, a figure that, by some estimates, will rise to over \$150 billion annually by 2038.³ In 2015, the total global cost of dementia was estimated to be \$818 billion, equivalent to 1.1% of global gross domestic product (GDP). The total cost as a proportion of GDP varied from 0.2% in low- and middle-income countries to 1.4% in high-income countries.¹⁶ Future costs for Alzheimer's threaten to bankrupt individual families and even national healthcare systems. It is estimated that if the number of patients increases as projected in the years ahead, the costs to care for them will exceed \$1.2 trillion annually in North America alone.¹⁶ This may pose an insurmountable fiscal challenge – one we cannot afford to ignore any further.

Despite being humankind's most prevalent dementia, the cause and cure of AD remain unknown. Yet the physical, emotional, and economic pressures continue to exert a devastating toll. AD is an immense and multifaceted disease that mandates urgent research, ranging from biomedical studies at the molecular level to health policy studies at the level of families and society. Challenging though it may be, if we are to reduce

harm to patients with dementia and their caregivers, we must have the compassion and courage to address this problem from an academic, health, social, financial, and legal perspective. In short, now is the time to sound the alarm about the impending Alzheimer's disease pandemic.

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