



What really causes  
Alzheimer's disease

HAROLD D. FOSTER

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*Dedicated to Grey Friar's Bobby*

## **AUTHOR'S NOTE**

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*There is a principle which is a bar against all information, which is proof against all argument, and which cannot fail to keep man in everlasting ignorance. That principle is condemnation without investigation.*

Herbert Spencer (1820-1903)

# WHAT REALLY CAUSES ALZHEIMER'S DISEASE: AN EXECUTIVE SUMMARY

There is currently a global Alzheimer's pandemic involving tens of millions of victims. In the USA alone, the number of those affected is expected to reach 14 million by 2050.<sup>1</sup> This suffering and the financial costs associated with it are unnecessary. Alzheimer's disease is caused by aluminum and is particularly common in those carrying the APO E4 allele(s), who are more susceptible to this toxic metal because they are less capable than the general population of removing brain beta-amyloid and tau proteins. As a consequence, such individuals are at higher risk of developing Alzheimer's disease, as these abnormal proteins build up in the brain and form neuritic plaques and neurofibrillary tangles. Naturally, this process occurs more often and most rapidly in regions that promote the deposition of beta-amyloid and tau. Such "harmful" environments are those in which drinking water is acidic, high in monomeric aluminum, and lack magnesium, calcium, and silicic acid. Under these circumstances, aluminum enters the brain and impairs various enzymes, including choline acetyltransferase, calcium/calmodulin kinase II, alkaline phosphatase, and phospholipase A2. The result of this process is the abnormal brain pathology seen in Alzheimer's disease patients and the disrupted biochemistry associated with it. In an earlier publication,<sup>2</sup> I called this explanation of the downward spiral, known as Alzheimer's disease, *Foster's Multiple Antagonist Hypothesis*.

Retrogenesis, the loss of abilities in cognition, coordination, behaviour, language, and feeding in the reverse order that they were acquired, occurs in Alzheimer's disease. This is, in part, because aluminum inhibits at least three membrane-bound enzymes, Na<sup>+</sup>K<sup>+</sup> ATPase, acetylcholinesterase, and, most interestingly, the myelin-specific enzyme 2'3'-cyclic nucleotide



phosphohydrolase.<sup>3</sup> As a result, it can cause rapid thinning of the myelin sheath<sup>4</sup> and increase its susceptibility to oxidative stress.<sup>5</sup> It seems very likely that these destructive processes are linked to demyelination and so to associated retrogenesis.

The APO E4 allele plays a key role in promoting Alzheimer's disease because of the inefficiency with which those possessing this genetic aberration can remove brain beta-amyloid and tau.<sup>6</sup> Genetically, however, there is more to Alzheimer's disease than the APO E4 gene. To date, four genes have been identified as playing a role in either early- or late-onset Alzheimer's disease: beta-amyloid precursor protein, presenilin-1, presenilin-2, and apolipoprotein E genes.<sup>7</sup> Workers have linked most of these variants to familial early-onset Alzheimer's, but the apolipoprotein E4 allele is a relatively common risk factor for developing late-onset Alzheimer's disease.<sup>8</sup>

Considerable progress has been made in interpreting the significance of such genetic variants. To illustrate, mutations in the presenilin-1 gene seem associated with increased superoxide production and greater vulnerability to amyloid beta peptide toxicity.<sup>9</sup> Interestingly, mutations in the presenilin genes, which are linked to more than 40 percent of all familial Alzheimer's cases, cause enhanced production of an abnormal form of beta-amyloid precursor protein.<sup>10</sup> This protein is longer than normal, aggregates more rapidly, kills neurons in culture more effectively, and precipitates preferentially to form amyloid plaques. The same elongated protein also is produced as a result of mutations in the gene encoding beta-amyloid precursor protein.

The literature suggests, therefore, that the gene variants that predispose to both early- and late-onset Alzheimer's disease do so because they either increase susceptibility to, or mimic, aluminum-related degenerative processes. That is, the genetic

mutations involved in promoting the development of Alzheimer's disease duplicate some of aluminum's deleterious impacts on the brain and, in so doing, encourage at least one of the following: the growth of neuritic plaques or neurofibrillary tangles, excessive free radical formation, and/or higher neural oxidative stress. Consequently, unfortunate individuals carrying any one of the genetic variants are much more likely to develop Alzheimer's disease, even if they are not exposed to the aluminum excess, or to the vitamin and mineral deficiencies, that are normally associated with its etiology.

Alzheimer's disease incidence appears to be rising faster than the population is aging. Obviously, such an increase cannot be due to any genetic cause. One does not have "epidemics" of genetic diseases, simply because the human genome does not change rapidly enough to trigger them. If, as the evidence strongly hints, Alzheimer's disease is becoming generally more common, it must be because the "harmful environments" that trigger it are now more widespread. There is no doubt that, globally, soils and water are becoming more acidic and, consequently, aluminum more soluble. Throughout the 20<sup>th</sup> and early 21<sup>st</sup> centuries, as a result of expanding fossil fuel consumption, ever increasing quantities of sulphur and nitrogen were emitted into the atmosphere. Here they were converted into sulphuric and nitric acids, elevating the acidity of subsequent precipitation.<sup>11</sup> Such acid rain has caused extensive damage to the environment at local, regional, and even global scales. It has been particularly problematic in northern and central Europe, eastern North America, and eastern China where it has been associated with many health costs.<sup>12</sup> Simultaneously, commercial fertilizers have been used with increasing frequency. These consist predominantly of nitrogen, phosphorus, and potassium. As a consequence of heavy crop yields, agricultural soils have been depleted of several minerals that are important for human health, including calcium and magnesium.

To illustrate, Marier and coworkers,<sup>13</sup> in *Water Hardness, Human Health and the Importance of Magnesium*, have pointed out how this mineral is becoming less and less common in the food we eat because of the fertilizers used in the “Green Revolution.” Food processing and cooking also remove minerals from food, and packaging and canning often add aluminum to it. As a result, most of the populations of the Western World appear to be very magnesium and often calcium deficient.<sup>14-15</sup>

Simply put, drinking water is becoming more acidic, and so aluminum is more soluble, foodstuffs contain fewer minerals as the result of commercial fertilizers, and many of the remaining minerals are removed by processing and cooking. We are creating, therefore, “harmful environments” that allow aluminum to reach the human brain more easily, where it then inhibits numerous crucial enzymes. It is not surprising that the highest known Alzheimer’s disease mortality rates in the world occur in southern Norway.<sup>16</sup> This is because the region’s drinking water is being made highly acidic by polluted rainfall, lacks calcium and magnesium because of the local geology, and contains high levels of aluminum.<sup>17</sup> From a scientific point of view, all these risk factors, with the exception of genetic inheritance, are relatively simple to mitigate. Alzheimer’s disease, in theory, therefore, is easy to avoid. There is no need for a pandemic, or the \$100 billion annual loss that it causes in the USA alone. Theoretically, it should be a relatively simple matter to pass legislation reducing levels of aluminum in, and promoting the addition of calcium, magnesium, and perhaps silicic acid to, drinking water. It would seem to be in the best interest of every government to save the billions of dollars spent in caring for Alzheimer’s disease victims. Unfortunately, politics is rarely so logical. Not only do governments show little interest in increasing the magnesium content of drinking water, they routinely allow the use of aluminum sulfate as a flocculant by water treatment plants. This additive reduces

the amount of sediment in the water supply, but simultaneously greatly increases levels of dissolved aluminum, especially if the water is acidic.<sup>18</sup>

The western diet promotes Alzheimer's disease in three distinct ways. Firstly, it tends to be deficient in calcium and magnesium,<sup>19-20</sup> making those who eat it very susceptible to aluminum toxicity. Secondly, many foods are canned, wrapped, and/or cooked in aluminum. The more acid the food, the more easily it dissolves this metal. Thirdly, maltol is added to many processed foods in an attempt to "improve" flavour. This additive facilitates the passage of aluminum through the blood-brain barrier. There can be little doubt also that the typical western diet is too low in many minerals. Consider, for example, magnesium. This occurs at relatively high levels in unrefined whole grain cereals and in green leafy vegetables, nuts, seeds, lentils, beans, and peas.<sup>21</sup> However, farmers do not routinely add magnesium to soils, so its levels are often relatively depleted in their crops. Since it is fairly soluble, food processing and cooking also often can greatly reduce magnesium levels in foods. To illustrate, the milling of whole grain lowers the magnesium content to only 20 percent of that initially present. Processing further reduces it, so that while one slice of whole wheat bread provides 24 milligrams of magnesium, a slice of white bread contains only 6 milligrams.<sup>22</sup> For such reasons, dietary intakes of magnesium have been declining for at least 100 years in the USA, falling from about 500 mg to 175-225 mg per day.

Fortunately, there is a great deal that individuals can do to reduce their chances of getting Alzheimer's disease. For most of those reading this book, the average day will begin with a shower. If the water used is acidic and deficient in calcium and magnesium, it is possible that it will be a source of aluminum that enters the body through the pores and nose. This exposure to aluminum is more likely if the water supplier uses

aluminum sulfate as a flocculant to remove sediment. Once dried off, most readers will smear their bodies with a layer of aluminum provided by antiperspirants and deodorants.<sup>23</sup> How much of this aluminum passes through the skin into the body is unclear, but McGrath<sup>24</sup> has argued that underarm shaving and frequent use of antiperspirants and deodorants appear to be linked to an early age of breast cancer diagnosis. British researchers<sup>25-26</sup> have provided evidence to support the feasibility of McGrath's hypothesis, reporting traces of parabens in every sample of tissue taken from 20 different breast tumours. Parabens are chemicals used in deodorants and other cosmetics that can mimic estrogen. The hormone estrogen is known to encourage breast tumour growth. Clearly, parabens can enter the body from deodorants and it is likely that aluminum can do the same. Deodorants with a herbal base do not usually contain these toxins.

Then comes breakfast. Tea, coffee, hot chocolate are usually made with water from the tap. It is important not to use soft, acidic water which is likely to contain monomeric aluminum. Most water supply companies will provide chemical analyses, allowing the assessment of the aluminum, calcium, and magnesium content of their product. If not, private companies can conduct such analyses relatively cheaply. If colas or fruit juices are drunk, they are likely to have come from cans. These are typically made of aluminum. The longer the drink has been in the can, the higher the aluminum levels in it are likely to be.<sup>27</sup> In addition to any aluminum it contains, hot chocolate is often "enhanced" with maltol, so increasing the likelihood that this metal will reach the brain. Similarly, tea brewed in acidic water or flavoured with lemon juice contains significantly higher levels of bioavailable aluminum than normal.<sup>28</sup>

After breakfast comes lunch, dinner, and a variety of snacks. Junk food, because it is so heavily processed, is usually a very

poor source of minerals, such as calcium and magnesium. As previously pointed out, the average British and North American diet contains less than half the calcium and magnesium required to avoid the associated deficiency illnesses, including Alzheimer's disease. The most effective way to address this problem is to eat many of the mineral enriched foods. These include salmon, sardines, broccoli, spinach, and bok choy, for example, which are all high in calcium.<sup>29-30</sup> Pumpkin seeds, almonds, Brazil nuts, and whole grain brown rice are good sources of magnesium.<sup>31</sup> Certain supplements, especially mineral ascorbates, also are excellent sources of both calcium and magnesium. Alacer Corporation, Foothill Ranch, California, a company with which I have no financial associations, provides excellent mineral ascorbate products. One tablet of Super-Gram II, for example, contains 4 percent of calcium and 8 percent of magnesium recommended daily allowance. Emer'gen-C is a fizzing drink mix that is pleasant to take when added to water. It provides 1,000 mg of vitamin C and 32 mineral complexes, including calcium and magnesium. Alacer's products were used in the joint Committee on World Health and Russian research projects that produced a marked reversal of memory loss in the elderly.<sup>32-34</sup>

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to this author by R. Dana and E. Dana, Committee for World Health, 20331 Lake Forest Drive, Suite C-15, Lake Forest, California 92630, USA.

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*Physicians, chemists, and theorists had by the early eighteenth century succeeded in making scurvy so complicated and obtuse that it would have been nearly impossible to get a useful or consistent diagnosis from a physician. The world of medicine was extraordinarily confused, with a great variety of physicians each offering his own personal variation on the humoral theory. To make universal sense of it is nearly impossible: indeed, the theories of many physicians were contradictory. With the layers of speculation building upon each other like the skins of an onion, and physicians tweaking their predecessors' theories to accommodate glaring inconsistencies, scurvy and its causes and cures became ever more fanciful and bewilderingly disconnected from reality.*

S.R. Brown, *Scurvy*, 2003

# WHO WAS I?

# 1

*LEAR: Does any here know me? This is not Lear.  
Does Lear walk thus, speak thus? Where are  
his eyes?  
Either his notion weakens, his discernings  
Are lethargied — Ha! Waking? 'Tis not so.  
Who is it that can tell me who I am?*

*FOOL: Lear's shadow.*

William Shakespeare, *King Lear*

Life expectancies have risen dramatically over the past century. As a consequence, in both the Developing and Developed World, the number of elderly has undergone an unprecedented increase, with the proportion of the very old in the population doubling in one generation. Globally, in 1950 there were 214 million people aged 60 or over; by 2025 there probably will be one billion, a more than four-fold increase.<sup>1</sup> Although, of course, there are major advantages associated with this trend, there are also serious costs. Not only are more people surviving into old age and, therefore, increasing their chances of developing dementia, but those who do so are living longer after its onset. In the USA, for example, Alzheimer's disease incidence, currently some 4.5 million, is expected to increase by 350 percent by the mid-21<sup>st</sup> century, clustering in those states with the highest numbers of retired "boomers." It is predicted, for example, that by 2025, 820,000 elderly Californians, 712,000 Florida residents, and 552,000 Texas will be suffering from Alzheimer's disease. Other states with high projected patient numbers include New York, Pennsylvania, and Ohio, that

together are expected to have a further 1,088,000 Alzheimer's cases.<sup>2</sup> The high costs of caring for these millions of demented elderly may wreak havoc on the health care system.

Gruenberg<sup>3</sup> termed this paradox the "failure of success" because it was a major problem that was largely attributable to progress in medical care. As he and his colleagues<sup>4</sup> pointed out, "the old man's friend, pneumonia, is dead—a victim of medical progress." While this is an oversimplification, pneumonia is certainly less common than it used to be, as are many other diseases that were previously fatal to the elderly. As a consequence, 5 to 6 percent of the USA population now has Alzheimer's disease or related dementia, some 4.5 million Americans. This figure is expected to rise to 14 million by 2050.<sup>5</sup>

Of course dementia is not limited to the USA. It has been estimated, for example, that as of the year 2000, approximately eight million people in the European Union Member States had Alzheimer's disease. Since this disorder accounts for some 50 percent of all dementia in people over 65, total estimates for dementia in Europe are closer to 16 million. As in the USA, the European population is aging rapidly and the number of senile dementia cases increasing dramatically.<sup>6</sup> Clearly, in the Western World, dementia is not a rare problem. Indeed, Katzman and colleagues<sup>7</sup> have argued that, in those aged over 75, new cases of dementia occur as frequently as myocardial infarction and twice as often as stroke.

## **RETROGENESIS**

Alzheimer's disease is the most common form of dementia in the Developed World, where it seems to affect some 5 percent of those aged over 65. It is not, however, limited to the elderly, but is found also in a much smaller percentage of the younger

population.<sup>8-9</sup> David Shenk,<sup>10</sup> in his interesting book *The Forgetting*, describes Alzheimer's disease as "death by a thousand subtractions." The scientific evidence appears to support this characterization. In 1980, for example, Barry Reisberg,<sup>11-12</sup> a neurologist from New York University, established the presence of an inverse relationship between the progressive stages of Alzheimer's disease and those of infant and childhood development. He demonstrated that as the symptoms of this form of senile dementia worsen the patient begins to lose abilities in cognition, coordination, behaviour, language, and feeding, in the reverse order that they were acquired in the early years of life. In the final stage of the disorder, the patient becomes infant-like, and can no longer walk, sit up without assistance, smile, or hold up their head. Reisberg<sup>13</sup> called this process of a thousand subtractions "retrogenesis," meaning "back to birth."

Although retrogenesis is not a perfect reversal, neurological tests do show that, as Alzheimer's disease progresses, there is an almost precise inverse relationship in neurologic reflexes, brain glucose metabolism, and EEG activity. As the disorder worsens, all these abilities decline. Such evidence led Reisberg to present a picture of the brain as a giant ball of string wound up in infancy and childhood but unwound by Alzheimer's disease. From birth and throughout childhood and beyond the ball grows rapidly, but in Alzheimer's it is unraveled in reverse, slowly but surely reducing the ability of the brain to function.<sup>14-15</sup>

Such a string analogy may not be far from the truth since researchers have found that Alzheimer's degeneration is linked to brain demyelination, that is, to the destruction of the white myelin sheath that insulates nerve axons and boosts their signal strength.<sup>16</sup> This destruction does not occur randomly but in the reverse order in which myelin was laid down early in life. To illustrate, in 1939 J.L. Conel, a Boston neuropathologist, began to dissect the brains of deceased children of a variety of

ages. In this way, he was able to trace the normal process of myelination, establishing that it begins first in the primary motor area which permits the infant gross movements of its hands, arms, upper trunk, and legs. Slightly later, myelination of the primary sensory area neurons of the parietal lobe occurs, so allowing gross touch sensations. This process of myelination continues throughout childhood and insulating myelin is laid down, for example, in the occipital lobe for visual acuity, and the temporal lobe for auditory processes. One of the very last brain structures to be covered with a layer of protective myelin is the hippocampus. This part of the brain is essential for consolidating immediate thoughts and impressions into longer-lasting memories that are then stored elsewhere. This late myelination of the hippocampus explains why children younger than three can rarely recall permanent memories and why adults cannot remember their earliest life experiences.

In Alzheimer's disease, brain damage appears to begin in the most recently and least-myelinated area of the brain, specifically in the hippocampus. As a consequence, the first symptoms of developing Alzheimer's are losses of recent memories. From the hippocampus, demyelination begins to impact on the frontal cortex, adversely affecting concentration, abstract thought and planning ability. This reverse myelination relentlessly continues, unwinding the "ball of string" in a very predictable manner until the primary motor area is finally affected and the late stage Alzheimer's patient is again infantile, unable to speak, sit up unassisted, or hold up their own head.<sup>17</sup>

## **CONSEQUENCES**

The only way to grasp the full meaning of Alzheimer's disease is to listen to someone who is suffering from it. At 57, Thomas DeBaggio was diagnosed with Alzheimer's disease.<sup>18</sup> At first he

saw this as a death sentence. “Tears welled up in my eyes uncontrollably; spasms of depression grabbed me by the throat. I was nearer to death than I anticipated.” After a few days of reflection, he decided that some good might come out of the diagnosis. “After 40 years of pussyfooting with words, I finally had a story of hell to tell.” The end result of this courageous decision is his book *Losing My Mind: An Intimate Look at Life with Alzheimer’s*, which is filled with journal quotations that chronicle his descent into hell as he passes further into the Alzheimer’s abyss. In his own words:

*This is an unfinished story of a man dying in slow motion. It is filled with graffiti, sorrow, frustration, and short bursts of anger. While the narrator suffers his internal spears, he tries to surround himself with memories in a wan attempt to make sense of his life and give meaning to its shallow substance before he expires. Although incomplete, the story is full of sadness and missed opportunity, a lonely tale of the human condition. Behind it is hope, the tortured luck of a last chance.<sup>19</sup>*

If you want to really learn what it is like to sit “at the edge of failure and hope,” read DeBaggio’s book.<sup>20</sup>

The process of reverse myelinization that is so characteristic of Alzheimer’s disease often destroys the life, not only of the affected patient, but also of those who love and care for them. This relationship has been described graphically by Shenk.<sup>21</sup>

*The unique curse of Alzheimer’s is that it ravages several victims for every brain it infects. Since it shuts down the brain very slowly, beginning with higher functions, close friends and loved ones are forced not only to witness an excruciating fade but also increasingly to step in and compensate for lost abilities. We all rely on the assistance of other people in order to live full, rich lives. A person with dementia relies increasingly—and, in the fullness of time, completely—on the care of others.*



This is no simple matter. The effects can be enormous and the term “caregiver’s dementia” is widely applied to describe the unfortunate symptoms, such as depression, fatigue, and forgetfulness, that accompany this thankless task. In the late 1990s, some 10 to 15 million Americans did their duty in such an unpaid role. Many were women who had just relinquished more conventional parenting when their children left the nest.<sup>22</sup> The statistics suggest that this problem will only worsen.<sup>23</sup> Currently, slightly more than half of Alzheimer’s patients receive home care.<sup>24</sup>

*Until a cure is found, the total number of Alzheimer’s cases is likely to double by 2030 and triple by 2050. Using Census Bureau population estimates and the rates of Alzheimer’s incidence by age bracket, determined in the East Boston Studies (i.e., 3.0% for ages 65-74, 18.7% for ages 75-84, and 47.2% for those 85 and older), the U.S. may expect a tremendous increase in the burden of caring for those stricken by this mind-robbing ailment. The ratio of Alzheimer’s cases for every 100 persons of working age may nearly double, from 2.8 cases per 100 working age persons to 5.3 cases.*

Not only does Alzheimer’s disease frequently devastate the lives of the family and friends of patients, but it also has major societal economic repercussions. The cost each year of caring for one Alzheimer’s patient suffering from the early, mild symptoms of the disease is estimated at \$18,408. This figure rises to \$30,096 when the symptoms become moderate and climbs to \$36,132 in the severest stage.<sup>25</sup> As a consequence, the total direct and indirect annual costs of Alzheimer’s disease in the USA alone is roughly \$100 billion. What does a figure like that really mean? I teach and conduct my research at a moderate-sized university in Canada with a student body of about 15,000. Its annual budget is roughly 0.25 percent of that spent in the USA each year to watch the health of 4.5 million Alzheimer’s

patients deteriorate. That is, the USA spends much more on Alzheimer's disease than Canada does on its entire system of higher education. Canada, of course, has problems of its own, with roughly 300,000 Alzheimer's patients who cost \$3.9 billion to care for in 1991. This figure is expected to rise to \$12 billion by 2030.<sup>26</sup>

It would appear from this brief description that one of the keys to solving the Alzheimer's jigsaw is an understanding of the demyelination that accompanies retrogenesis. What is it that is driving the process and so progressively reversing the gains made by the brain in infancy and childhood? It is clear that the disease cannot simply be a form of accelerated aging because many Alzheimer's patients with deteriorated cognitive ability still have excellent physical health.<sup>27</sup> Similarly, it is not due to any "hardening of the arteries," that is to cerebral arteriosclerosis, although this condition is more likely to be associated with stroke or multi-infarct dementia. For this reason, the use of hyperbaric oxygen chambers to treat Alzheimer's disease has proven unsuccessful.<sup>28</sup>

While slow viruses and prions have been identified as the causes of some brain disorders, such as Kuru and variant Creutzfeldt-Jacob disease,<sup>29</sup> none have been unequivocally isolated from the brains of former Alzheimer's patients. In addition, there is no evidence that Alzheimer's disease is infectious and so can be transmitted among humans. Similarly, with a few exceptions, there is little evidence to suggest that non-human primates can be infected with it.<sup>30</sup> The distribution of Alzheimer's disease is also very unlike that caused by an infectious agent, being both geographically extremely variable but relatively spatially constant over time.<sup>30</sup>

Similarities in the nature of the degeneration of the central nervous system occur in Alzheimer's disease, Guamanian

amyotrophic lateral sclerosis, and Parkinsonism with dementia. This suggests that all three illnesses may have a common pathogenic mechanism.<sup>32</sup> Clues about which aspects of the environment may be acting as triggers have been provided by biopsies that reveal abnormally high levels of calcium, silicon, and aluminum in the central nervous systems in patients dying from all three disorders.<sup>33-35</sup>

## SUMMARY

Although there is no evidence that autosomal dominant inherited mutated genes cause late-onset Alzheimer's disease, it has been shown<sup>36</sup> that this illness is more common in individuals who have inherited one or two copies of the apolipoprotein (APO E4) allele on chromosome 19. This gene directs the manufacture of the APO E protein that carries blood cholesterol throughout the body. In contrast, the APO E3 allele is the most common version seen in the general population, where it seems to play a neutral role in the development of Alzheimer's disease.<sup>37</sup> The fundamental problem with the slow and tedious search for the cause(s) of Alzheimer's disease is that it is completely dominated by experts.<sup>38</sup> That means that, as Shenk<sup>39</sup> pointed out, the research is "so intensely specialized that few individual scientists appear to even be working on the problem of Alzheimer's disease *per se*. It was more like each was unearthing a single two-inch tile in a giant mosaic. By themselves, these individual experiments were so narrowly focused that they were far removed from a comprehensive understanding of the disease." What is really needed is not more detailed scientific research but a holistic attempt to put together the existing pieces of the Alzheimer's mosaic, so that it becomes possible to forestall the impending wave of future Alzheimer's patients and the enormous personal and social costs associated with it. This volume is an attempt to achieve that goal.

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*Words ought to be a little wild for they are the assault of thoughts on the unthinking.*

John Maynard Keynes (1883-1946)

## IN THE BEGINNING: A HISTORY

*I am going to tell the story of my life  
in an alphabet of ashes.*

Blas De Otero, *Twenty Poems*

In 1998, *Neurogenetics*<sup>1</sup> reported that Manuel Graeber and his colleagues from the Max Planck Institute for Neurobiology in Martinsried, near Munich, had discovered over 250 slides made from samples of the brain of Auguste D. These slides had been housed for almost a century in a basement of the University of Munich. This find was big news. Researchers had been looking for Auguste D.'s brain samples since 1996, when her original hospital file had turned up at an institute of the University of Frankfurt.<sup>2</sup> Why was the discovery of tissue slides from a patient who died in 1906 so significant to Science?

### THE FIRST CASE

Auguste D. was first admitted to Frankfurt's *Hospital for the Mentally Ill and Epileptics* in 1901. Even though she was only 51, Auguste D. was severely divorced from reality, suffering from disorientation, hallucinations, and paranoia.<sup>3</sup> Her speech also was extremely limited. One of her physicians in Frankfurt, Dr. Alois Alzheimer, had been a doctor at the hospital for some 13 years but was still baffled by her case and so took an unusual interest in it. Even after a career move to the Royal Psychiatric Clinic in Munich in 1903, Alzheimer continued to



follow the progression of Auguste D.'s illness from a distance. As a consequence, when she died in April 1906, the director of the Frankfurt hospital sent her brain to Alzheimer, who used it to produce the recently rediscovered 250 sample slides.<sup>4</sup> Alzheimer studied these slides in detail, presenting his initial results at a psychiatry meeting in Tübingen 7 months later. An assessment of Auguste D.'s case was subsequently published by him in 1907. These events ensured a place in medical history for both Auguste D. and Dr. Alois Alzheimer. Auguste D. is remembered as the first patient with documented Alzheimer's disease, while her physician's name will be eternally linked to this terrible form of senile dementia.<sup>5</sup>

What was it about Auguste D.'s brain samples that Alzheimer found so striking and unusual? He noticed something in the slides that was extremely rare—gum-like clumps outside some cells and abnormal collections of proteins inside others, that is plaques and tangles respectively. A fresh look at the recently rediscovered Auguste D. slides confirms Alzheimer's claims. Her cortex displayed what are now accepted as the classic pathological signs of the disease named after him: amyloid plaques and neurofibrillary tangles. Indeed, neurofibrillary tangles were described for the first time ever in this brain.<sup>6</sup>

## **HISTORY OF DEMENTIA**

It is clearly established, then, that Alzheimer's disease existed in 1901. However, there are several significant questions about the history of this illness that should be asked, even though it may not be possible to answer them. For example, "Was Auguste D. one of the first in a wave of patients suffering from a new disease, or had millions of previous cases (of what would from now on be called Alzheimer's disease) been dismissed as simply age-related, that is senile dementia?"

In 1901 there was certainly nothing new about dementia in the elderly. This condition had been known by the Greeks as *morosis*, and as *oblivio* and *dementia* by the Romans. In Middle English it was known as *dotage*, in French it was called *démence*, and in 18<sup>th</sup> century English it was categorized as *fatuity*.<sup>7</sup> The term *senile dementia* itself was first coined by the French psychiatrist Jean Étienne Esquirol in 1838, who wrote: “Senile dementia is established slowly. It commences with enfeeblement of memory, particularly the memory of recent impressions.”<sup>8</sup>

Classical literature is also full of references to the elderly demented. The Roman poet Juvenal, for example, wrote in the 1<sup>st</sup> century AD: “worse than any loss in body is the failing mind which forgets the names of slaves, and cannot recognize the face of the old friend who dined with him last night, nor those of the children whom he has begotten and brought up.”<sup>9</sup> Even earlier, in the 4<sup>th</sup> century BC, the Greek historian Xenophon wrote in his *Memorabilia*: “haply [by chance] I may be forced to pay the old man’s forfeit—to become sand-blind and deaf and dull of wit, slower to learn, quicker to forget, outstripped now by those who were behind me.”<sup>10</sup> Even the *Bible*, in Ecclesiasticus chapter 3, verses 12-13 encourages the young to understand the mental decline often seen in the elderly with this advice: “O son, help your father in his old age, and do not grieve him as long as he lives / even if he is lacking in understanding, show forbearance.”

There is no doubt, therefore, that dementia has been a curse of many of the elderly for millennia, providing fodder for authors as diverse as Euripides, Chaucer, Shakespeare, Chekhov, Trollope, Darwin, and Sir Walter Scott.<sup>11</sup> What is not so obvious, however, is whether the senile dementia characterized by these and other scribes was actually Alzheimer’s disease. There are, for example, more than 70 known types of dementia.<sup>12</sup>

Even today, in some ethnic groups or at specific locations, Alzheimer's disease might not be the most common form of this illness amongst the elderly. To illustrate, in Japan, consistently high incidence rates have been recorded for multi-infarct dementia, caused by many small strokes, while those for senile dementia of Alzheimer's type appear considerably lower than in Europeans.<sup>13</sup> Similarly, in China, there are marked regional variations in specific dementia prevalence. Vascular dementia, for example, predominates in Beijing, yet Alzheimer's disease is the major form of dementia experienced in Shanghai.<sup>14</sup>

## **ANCIENT ALZHEIMER'S DISEASE?**

While it is very probable that many of the mentally declining elderly described in the classical and more recent literature were suffering from Alzheimer's disease, the evidence is not conclusive. What is required for absolute proof are ancient brains that display the plaques and tangles that define Alzheimer's disease. The most appropriate place to look for these would appear to be mummies, although many of those ancient relics were deprived of their brains during preservation. Complicating the search is the relatively young age at death of most mummies, a reflection of the shorter life expectancies of earlier civilizations. In a *Lancet* article, for example, Dr. Rosalie David, Director of the Egyptian Mummy Research Project at the Manchester University Museum,<sup>15</sup> describes studying the long departed with computed axial tomography (CAT) scans, electron microscopy, and other highly sophisticated techniques. This research was designed to discover the nature of diseases and disorders amongst Ancient Egyptians. Interestingly, they displayed few indications of modern day scourges such as tuberculosis, syphilis, and cancer. In contrast, many Egyptian mummies had been infected by malaria such as *Plasmodium*

*falciparum*, which causes malaria, and *Echinococcus granulosus*, often linked to liver and lung disease. *Trichinella*, a parasite that causes trichinosis and which is usually contracted through eating pork or other infected meats, was also found to have been common in Ancient Egypt. *Schistosoma haematobium*, the parasite responsible for the current schistosomiasis pandemic, has been identified in two mummies.<sup>16-17</sup> It must be admitted, however, that Egyptian dead are likely to be a very poor source of information about Alzheimer's disease, since their brains were removed through their noses during the mummification process.<sup>18</sup> Since the Egyptians thought intelligence arose from the heart, ancient embalmers typically threw away the brain.

The Egyptians, of course, were not the first to practise mummification. The oldest mummies known are Chilean, created by the Chinchorro culture, predating their Egyptian counterparts by thousands of years. The Chiribaya, a pre-Columbian coastal people who lived in what is now the desert of southern Peru from 950 to 1350 AD, also mummified their dead. Beyond this, many mummies have been discovered in China and elsewhere.<sup>18</sup> A *PubMed* search using two key words, "disease" and "mummies," revealed 61 matching publications. These described everything from evidence of prehistoric tuberculosis in America<sup>19</sup> and China<sup>20</sup> to louse infection in the Chiribaya.<sup>21</sup> A similar search based on "Alzheimer's" and "mummies" found no matches. Similarly, in the indexes of two books on the topic, specifically *Mummies, Disease and Ancient Cultures*, edited by Thomas Cockburn and colleagues,<sup>22</sup> and *Disease*, authored by Joyce Filer,<sup>23</sup> no mention of Alzheimer's disease was found. While none of this negative evidence establishes that the senile dementia recorded in the classical literature for millennia was not Alzheimer's disease, the crucial physical evidence that it *was* appears to be missing. At best, the case remains "unproven."

## CHANGES OVER TIME

A second highly significant historical question that needs to be asked is “Has the age-standardized prevalence of the disease remained constant since Alois Alzheimer’s discovery of it, or is Alzheimer’s disease becoming more common in specific age groups?” This is a very important issue because, if this form of senile dementia is predominantly genetic in origin, age-specific incidence and mortality rates will remain relatively constant. If genes are destiny, we cannot have pandemics of Alzheimer’s disease because the human genome does not change rapidly enough to cause any significant increase in the number of cases in specific age groups. This does not mean that as the population ages, the number of people developing Alzheimer’s disease will not rise but, if the disease is essentially genetic, there will be no significant increase in the probability that someone aged 85, for example, will be diagnosed with this type of dementia. In contrast, if the most significant causal variable in Alzheimer’s disease is environmental or social, then rapid increases in this form of senile dementia could be triggered by environmental and/or social change, even in individuals who formerly would have avoided it.<sup>24</sup>

Despite the fact that Alzheimer’s disease was recognized as a distinct entity in 1907, it has been the subject of very few large scale epidemiologic, or geographical studies. The difficulty of accurate diagnosis is one of the major reasons for this lack. Once dementia has been established, and this in itself is not necessarily easy, the specific disease underlying it must be identified. The problem is compounded by the fact that there are more than 70 conditions that have been accepted as potential causes of dementia.<sup>25</sup> When studying a large population, researchers are faced with the daunting task of ruling out all of these other possible disorders, in order to identify patients with Alzheimer’s disease. Despite sophisticated diagnostic

techniques, medical researchers must still rely on such problematic diagnosis by exclusion “until the characteristic lesions of Alzheimer’s disease can be documented on pathological examination of the brain.”<sup>26</sup> Since so few autopsies are conducted on the elderly, it is very difficult to obtain accurate data capable of establishing variations in the incidence of Alzheimer’s disease over time. As a result, it is hard to determine how much, if any, the risk of developing the disease has changed in specific age groups since it was first recognized in the early 20<sup>th</sup> century by Alzheimer.<sup>27</sup>

This problem of diagnosis without autopsy does not mean that there have been few surveys of the demented. Indeed, in 1998, Ineichen<sup>28</sup> identified over 100 epidemiological surveys of dementia published from a wide variety of countries. What can all this information tell us about the age-adjusted incidence of Alzheimer’s disease? Is it increasing? This is still a very difficult question to answer with any certainty. There can be no doubt, for example, that the age-adjusted mortality rates for Alzheimer’s disease have risen over the past decade in both Arizona<sup>29</sup> and Missouri.<sup>30</sup> However, how much this is the result of a true increase in incidence of the disease in particular age groups, and how much it simply reflects improved diagnosis, changes in public and physician attitudes towards Alzheimer’s disease, alterations in the coding and classification of dementia, and decreases in other leading causes of death is very unclear.<sup>31</sup>

Studies of temporal change in dementia incidence really require repeated surveys of the health of large populations. As a consequence, they tend to be rare because they are complex, costly, and involve extended fieldwork over long periods of time. The most robust such study comes from the Swedish Island of Lundby<sup>32</sup> whose entire population of approximately 2,500 was examined several times between 1947 and 1972.

The established incidence rates for dementia on this island were 0.7 percent for men and 0.5 percent for women in their 70s, and 1.9 percent and 2.5 percent for males and females, respectively, aged 80 and over. However, much more interesting than the actual dementia incidence rates was the fact that these surveys established that such rates were lower in the second time period (1957-1972) than they had been in the first (1947-1957) for both genders and at all levels of dementia severity. Hagnell and colleagues<sup>32</sup> attributed this decline to improved economic security which had brought with it more social activity and better diets.

Nevertheless, more recent studies tend to hint that Alzheimer's disease may be becoming a more common cause of death amongst specific age groups, that is that its age-adjusted annual mortality rate may be rising. In the USA,<sup>34</sup> for example, Alzheimer's disease was recorded as the underlying cause of death for 21,397 persons in 1996, contributing to the mortality of an additional 21,703. The age-adjusted death rate for this disease in the USA rose rapidly from 1979 to 1988, changed little from 1988 to 1992, and increased again from 1992 to 1995. It then appeared to level off once more. In 1999, the Centers for Disease Control and Prevention<sup>35</sup> attributed 44,509 deaths to Alzheimer's disease in the USA, but much of this increase stemmed from abolition of the term "presenile dementia" as a possible cause of death. Nevertheless, the most recent information from the US Department of Health and Human Services<sup>36</sup> claims a 5 percent increase in the age-adjusted rate of Alzheimer's disease death for the time period 2000 to 2001, suggesting that this disease may be increasing in specific age groups.

While it is undoubtedly true that a heightened awareness may have encouraged USA physicians to diagnose cognitive impairment as Alzheimer's disease more often in 1996 than in 1979,

USA age-adjusted mortality rates for senile and presenile dementias also rose rapidly at the same time. The associated decline in deaths recorded as due to senility could not totally account for these trends. In conclusion, it is unclear how much of the recent increase in USA age-adjusted Alzheimer's disease death rates have been the result of methodological changes and how much they have been caused by real growth in the prevalence of this illness. However, the apparent increase in mortality from Alzheimer's disease at specific ages recorded in the USA<sup>37</sup> is consistent with very similar trends seen in Australia,<sup>38</sup> Canada,<sup>39</sup> England,<sup>40</sup> and Norway<sup>41</sup> where Alzheimer's disease death rates also appear to have risen. The best present answer that can be given truthfully to the question, "Is an 80 year old man or woman in the USA or Europe more likely to develop Alzheimer's disease now than they would have been in 1907 when Alois Alzheimer first identified the disease?" is "Probably."

## **SUMMARY**

Studies of the history of Alzheimer's disease are bedevilled by problems of identification. Although a wide range of high and low technology<sup>42-43</sup> has been developed to aid in its diagnosis, the most definitive way of establishing the presence of this disorder is still that which was first pointed out by Alois Alzheimer—extensive brain deposits of amyloid plaques and neurofibrillary tangles. As a consequence of this difficulty with diagnosis, and since there are some 70 other types of dementia, it is very hard to know whether historical references to senile dementia really referred to Alzheimer's disease. There is no evidence from mummies, known to this author, that suggests that they did.

It is almost as difficult to establish whether age-adjusted incidence and mortality have been rising since 1907, when



Alzheimer first identified this form of dementia. This is due to the impact of improved diagnosis, changes in public and physician education about and attitudes towards Alzheimer's disease, alterations in the coding and classification of dementia, and decreases in other significant causes of death. As a result, while the prevalence of Alzheimer's disease is clearly rising rapidly as the population ages, it is not certain whether the probability of a specific individual developing this form of dementia, at any given age, is also increasing.

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*Oh God, that men should put an enemy in their mouths  
to steal away their brains!*

William Shakespeare, *Othello*

## PLAQUES AND TANGLES

What were the plaques and tangles that Dr. Alois Alzheimer<sup>1</sup> saw in the slides he made from portions of Auguste D's brain? There is no doubt that Alzheimer's disease patients have an abundance of two abnormal structures in their brains, both amyloid plaques and neurofibrillary tangles.<sup>2</sup> These are particularly common in those regions of the brain that are very important in the creation of memory. Plaques consist mainly of dense, insoluble deposits of protein and cellular material that build up around and outside neurons. Tangles are twisted, insoluble fibres that develop inside nerve cells. While such structures can be found in limited numbers in the brains of many healthy elderly people, they are present to a much greater degree in those who have shown the symptoms of Alzheimer's disease.<sup>3</sup>

During the 1970s, scientists discovered that the dominant protein in such plaques was beta-amyloid. In the normal brain, a larger protein—the amyloid precursor protein—is broken down into three smaller protein fragments known as alpha-amyloid, beta-amyloid, and gamma-amyloid.<sup>4</sup> In those individuals with

Alzheimer's disease, when amyloid precursor protein breaks down it creates a disproportionate amount of beta-amyloid but less alpha-amyloid and gamma-amyloid protein than usual. This excess of beta-amyloid protein overwhelms the brain's capacity to remove it and so it accumulates as insoluble gum-like plaques,<sup>5</sup> which may also contain other molecules, neurons, and non-nerve cells.<sup>6</sup>

Such plaques "gum up the works" by damaging the connection points, that is the synapses, between neurons and, as a consequence, interfere with such cells' ability to communicate. In Alzheimer's disease, early plaques develop in the hippocampus, a brain structure involved in encoding memories, and also in other parts of the cerebral cortex that are necessary for thought and decision making. As the disease progresses, additional plaques form in the frontal lobes of the brain. The more severe the symptoms of Alzheimer's disease, the more plaques will typically be found in the patient's brain during autopsy.<sup>7</sup> Such beta-amyloid plaques also trigger an inflammatory response. Part of this process involves the creation of oxygen free radicals—highly reactive molecules which can damage or kill other cells by creating holes in their membranes or binding to their DNA and interfering with survival. This plaque-related inflammatory process appears to destroy large numbers of brain cells in Alzheimer's patients and its effects are obvious in stained brain sections.<sup>8</sup> This could be why taking anti-inflammatory drugs, for other health problems, may accidentally reduce the probability of developing Alzheimer's disease.

Healthy neurons have a support structure that is made up, in part, of microtubules that act like tracks, guiding nutrients and other molecules from the cell body to the ends of the axon and back again.<sup>10</sup> The stability of these microtubules is maintained by a type of protein known as tau. In patients with Alzheimer's disease, tau becomes chemically abnormal and begins to pair

with other threads of tau and become tangled. As this happens, neuron microtubules disintegrate. These “tangles” prevent the movement of nutrients and other molecules to the nerve endings of the neurons, and as a result, communication malfunctions can occur, often followed by cell death. Tangles initially interfere with the functions of the brain’s temporal lobe, causing memory loss and difficulties in reading and writing. As plaques and tangles begin to appear in the frontal lobes, personality disorders and other symptoms appear. While tangles can be seen also in the brains of healthy older people, they are relatively rare. In Alzheimer’s patients, the worse the symptoms, the more common tangles are usually found to be on brain autopsy.<sup>11</sup>

## **NUCLEUS BASALIS OF MEYNERT**

Plaques and tangles do not seem to be the only cause of Alzheimer’s-related neuron death. Certain neurons found at the base of the brain known as the Nucleus Basalis of Meynert, appear to die in Alzheimer’s disease without any evidence of the interference of plaques or tangles. Such neurons produce acetylcholine, a chemical messenger used in communication between neurons. Normally acetylcholine-manufacturing neurons have long branches that reach into the hippocampus and cortex and are thought to play an important role in learning and memory. Their death in Alzheimer’s disease means that less acetylcholine is available to the brain, probably interfering with both its memory and learning capacity.<sup>12</sup>

## **WHITE MATTER: MYELIN**

The brain looks a little like an orange. An outer layer of grey tissue surrounds a whitish core. This outer exterior is formed

of neurons and their associated neurites, short protrusions that are used to communicate with neighbouring nerve cells. The grey matter then can be viewed as the brain's central processor. Neurons, however, also send information through the brain to the central nervous system by transmitting electrical signals that travel over long appendages termed axons. These axons are covered by myelin, an insulating sheath of fat that speeds signal transmission. The brain's white matter is largely composed of such myelin.<sup>13</sup>

Interestingly, because memory loss is so typical of Alzheimer's disease, most research has focussed on the grey matter of the brain, especially of plaques and tangles. However, it is becoming evident that in Alzheimer's disease myelin proteins, lipids, and cholesterol are significantly reduced.<sup>14-16</sup> This loss is termed demyelination and appears to play a significant role in retrogenesis, the decline of the patient's abilities in the reverse order to which they were developed during childhood and infancy.<sup>17</sup>

## **GENE DREAMING**

It is obvious that Alzheimer's disease involves a complex biochemical collapse of the brain that appears to proceed with a strange, perverted logic. Abilities are lost in the reverse order to which they were acquired, as plaques and tangles damage the grey matter, myelin degrades in the white matter, and acetylcholine-producing neurons are killed at the base of the brain. This destruction is accompanied by tissue shrinkage, known technically as progressive cerebral atrophy, a process that can be monitored using computer-enhanced volumetric magnetic resonance imaging scans.<sup>18</sup> Undoubtedly, the key question to be asked is "What is the root cause of this brain disintegration?"

The most extreme of the geneticists believe that the misery of Alzheimer's disease is all preordained; that is, it has a simple Mendelian causality. If you have the "wrong" genetic aberration, you will develop the disease, unless you die earlier in life from some other cause.<sup>19</sup> This is the position taken by Rudolph E. Tanzi, director of the Genetics and Aging Research Unit at the Massachusetts General Hospital.<sup>20</sup> Based on recent findings of 12 new potential sites for Alzheimer's genes, he claims that within 50 years, patients will be routinely screened for these genes, and be given prescription drugs tailored to reduce their identified genetic risk.

Speaking at the 2003 annual meeting of the American Association for the Advancement of Science (AAAS), held in Denver, Colorado, Tanzi said:

The genetic underpinnings for up to 70 percent of Alzheimer's cases remain unsolved. This research lays the ground work for identifying genes that will allow us to reliably predict the disease before it strikes, giving us new clues about biological causes of disease so that we can help prevent it. The ultimate goal is to custom-make drugs to address our own genetic properties. Our laboratory's goal of early prediction-early prevention of this insidious neurological disorder will likely emerge in the future as the preferred means for treating cancers, diabetes, heart disease, and other common yet complex genetic disorders that challenge the health of our elderly population. Like Alzheimer's, all of these disorders involve, on one hand, rare gene mutations that cause early onset forms of the disease and, on the other hand, common gene variants that increase susceptibility to these diseases as we age.<sup>21</sup>

So far, however, the evidence that tangles, plaques, myelin degradation, and the other pathologic symptoms of Alzheimer's disease have a simple Mendelian causality is relatively poor.



In total, four genes have been identified that appear to play some role in Alzheimer's disease. Three of these have been linked to the relatively rare early-onset type, while the fourth seems to increase sporadic Alzheimer's disease risk in people as they age.<sup>22</sup>

More specifically, only a small minority of patients, between 1 and 7 percent, suffer from the early-onset form of Alzheimer's disease.<sup>23</sup> Those who do can begin to show symptoms as early as 30 years of age. Early-onset Alzheimer's disease appears to have links to specific rare genetic aberrations that occur on chromosome 1, 14, and 21. However, the great majority of Alzheimer's disease patients do not begin to display symptoms until they reach the age of 65 and suffer from the much more common, that is the sporadic, type of the disorder.<sup>24-25</sup>

This form of Alzheimer's disease seems linked, to some degree, to a gene in chromosome 19 called the APO E gene, which codes for apolipoprotein E. This protein is involved in the cellular movement of cholesterol throughout the body. There are three slightly different types (known as alleles) of the APO E gene, namely APO E2, APO E3, and APO E4. Everybody has inherited two copies of this gene, one from each parent. The E3 variant is the most common and occurs in between 40 and 90 percent of the populations of particular regions; E2 and E4 are less common, being present in 2 percent and 6 to 37 percent of people respectively.<sup>26</sup> It has been demonstrated that the probability of developing sporadic late-onset Alzheimer's disease is much higher in those possessing the EPO E4 allele. Indeed, anyone who has inherited copies of the APO E4 allele from both parents has a 15 times greater risk of developing sporadic Alzheimer's disease than someone without this form of the APO E gene.<sup>27</sup> Consequently, in Alzheimer's patients, carriers of the APO E4 are common, with this allele being present in approximately 40 percent.<sup>28</sup>

## SUMMARY

Major pathologic changes occur slowly but surely, often over a decade or more, in the brains of Alzheimer's patients. Plaques and tangles form in the grey matter, myelin degenerates in the brain's white matter, and acetylcholine-producing neurons are killed at its base. How much of this destruction is genetically controlled is as yet unclear, but as far as the mitigation of the Alzheimer's disease pandemic is concerned, genetics has so far promised a great deal more than it has delivered.

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## PUTTING THE DISEASE IN ITS PLACE

*An invasion of armies can be resisted, but not an idea whose time has come.*

Victor Hugo, *Histoire d'un crime* (1852)

For millennia, it has been recognized that patterns of human and indeed animal disease generally reflect the nature of both the environment and of behaviour. In his book *On Airs, Waters and Places*, the ancient Greek physician Hippocrates,<sup>1</sup> for example, wrote:

*Whoever wishes to investigate medicine properly, should proceed thus: in the first place to consider the seasons of the year, and what effects each of them produces... Then the winds, the hot and the cold, especially such as are common to all countries, and then such as are peculiar to each locality. We must also consider the qualities. In the same manner, when one comes into a city to which he is a stranger, he ought to consider its situation, how it lies as to the winds and the rising of the sun: for its influence is not the same whether it lies to the north or to the south, to the rising or to the setting sun. These things one ought to consider most attentively, and concerning the water which the inhabitants use, whether they be marshy and soft, or hard, and running from elevated and rocky situations, and then if saltish and unfit for cooking, and the ground, whether it be naked and deficient in water, or wooded and well watered, and whether it lies in a*

*hollow, confined situation, or is elevated and cold: and the mode in which the inhabitants live, and what are their pursuits, whether they are fond of drinking and eating to excess, and given to indolence, or are fond of exercise and labour, and not given to excess in eating and drinking.*

## **THE HEALTH FIELD CONCEPT**

Medical geographers, including myself, spend a great deal of time and effort studying disease patterns and attempting to discover what controls them.<sup>2-6</sup> It is obvious that illnesses do not occur uniformly around the globe. They display spatial patterns that reflect the influences of four major variables: human biology, environment, lifestyle, and medical care. The first of these controlling variables, human biology, includes personal characteristics such as gender, age, and genetics over which we have no control, but which, nevertheless, have a great influence on our susceptibility to illness. To illustrate, breast cancer is far more common in women than men, while prostate cancer occurs in males alone. The incidence of both diseases increases with age. Environment also has a significant influence on patterns of disease, through such characteristics as attitude, climate, the chemical composition of soils, foods, and drinking water, and the presence or absence of particular pathogens and their vectors. The milieu also has disease-related social dimensions that include population density, housing design and construction, the nature of the infrastructure, and industrial and agricultural processes and pollutants. To some degree, especially through mobility, we can control the health impacts of such environmental variables. Individuals also greatly affect their own health through lifestyle choices.<sup>7</sup> Maps showing where illnesses occur and what people are dying from clearly reflect self-selected risk factors such as promiscuity,

smoking, over-consumption of alcohol and food, lack of hygiene and failure to exercise.<sup>8</sup> Given the multiple threats to health from certain aspects of human biology, environment, and lifestyle, it is hardly surprising that every society develops some provisions for health care. Obviously, choice of the adopted medical system(s) has a major impact on which diseases are considered curable and which are not. As a result, medical care is also reflected in geographical patterns of death and disease.

As a geographer I am very biased. It is my belief that until we can convincingly establish why a particular disease is common in some regions and very rare or absent from others, we have achieved very little of intellectual significance. This chapter, then, examines variations in the global and regional patterns of Alzheimer's disease and attempts to identify which aspects of human biology, environment, lifestyle, and medical care are responsible for them. That is, it is a review of what medical geographers and epidemiologists can tell us about this form of dementia.

If the development of sporadic (late-onset) Alzheimer's disease was largely a consequence of genetic inheritance, then two geographic corollaries follow.<sup>9</sup> Firstly, since the APO E4 form of the gene (which is thought to predispose to sporadic Alzheimer's disease) is apparently already very widely distributed throughout the entire human population, this form of dementia ought to display relatively similar, random patterns of age-adjusted mortality. Incidence and prevalence of Alzheimer's disease, in contrast, would be expected to vary with global differences in life expectancy. That is, if a widely distributed genetic aberration were the major cause of Alzheimer's disease, this form of dementia would occur with roughly the same frequency everywhere. However, cases would peak in those areas with disproportionately high populations of elderly.

Secondly, if a disease is the result of a globally dispersed genetic characteristic, migration should not cause a significant alteration to its incidence or mortality. This is because the dominant risk factor(s) would be internal. What this means, for example, is that amongst the same age groups, Alzheimer's disease ought to be as common in Japan as it is in American-Japanese living in the USA.

These two corollaries allow the current belief that the major risk factor(s) in Alzheimer's disease are genetic to be tested using geographical evidence. This goal can be achieved by comparing global and regional spatial patterns of Alzheimer's disease incidence and mortality with those that one would expect to see if the disease were largely genetic in origin. It must follow that if the geography of Alzheimer's disease is very like that implied by the genetic hypothesis, then there is a strong probability that the genetic model is correct. Naturally, the reverse is also true. If implied and real geographies greatly differ, it is impossible for the genetic hypothesis for sporadic Alzheimer's disease to be valid.<sup>10</sup>

## **SPATIAL DISTRIBUTION: GENETIC COROLLORY ONE**

The best available reviews of the global geography of dementia are probably those of Henderson<sup>11</sup> and Ineichen.<sup>12</sup> If you would like to read detailed overviews about what is known, these publications are where to start. Ineichen, for example, identifies over 100 epidemiological surveys that have been conducted over the last 55 years from countries around the globe. Rather than attempt to repeat such a review of dementia here, all that will be presented are a few highlights related to Alzheimer's disease. According to Ineichen,<sup>13</sup> "Alzheimer's has been shown to be the commonest sub-type [of dementia] in most parts of the world, but vascular or multi-infarct dementia has been

reported more commonly from Russia, Japan and China, and in atypical surveys in North America.” While Ineichen is not sure whether these geographical differences really exist, it seems likely that they do, but may be altering with changing diets and pollutant levels. The reality of such global geographical variations in the incidence and prevalence of both Alzheimer’s disease and multi-infarct dementia (vascular dementia) have been established, for example, by Chinese dementia researchers who have shown that multi-infarct is the dominant form of dementia in Beijing, while Alzheimer’s disease is the more common dementia in Shanghai.<sup>14-15</sup> Such regional variations in the incidence of Alzheimer’s disease are not limited to China. In a rare whole country study, Sulkara and coworkers,<sup>16</sup> for example, established that Alzheimer’s disease was significantly more prevalent in the north and east of Finland than elsewhere in the country. The reasons for this pattern were unknown.

Clearly, there are great variations in the incidence and prevalence of Alzheimer’s disease at the local level. This form of dementia, for example, appears particularly rare in Maracaibo, Venezuela. Molina and colleagues,<sup>17</sup> for example, have described the results of autopsies conducted in four large hospitals in that city on brains that included those of all known dementia patients. In the first of these studies covering a 10 year period, 3,657 successive autopsies revealed that 86.7 percent of such patients had suffered from vascular dementia and the rest from other forms of dementia which did not include Alzheimer’s disease. Six years later, a further 611 adult brains had been autopsied, including all of the 39 dementia patients who had died in any of the four hospitals during the period 1992 to 1998. Once again, vascular dementia (84.6 percent) had dominated; 5 (12.8 percent) showed evidence of some other form of dementia, but not Alzheimer’s disease. Only one brain (2.6 percent) displayed plaques and tangles, that is the diagnostic form of damage seen in Alzheimer’s disease. Taken together,



these two hospital-based studies cover over 15 years of autopsied dementia deaths in Maracaibo, a city that has a population of some 650,000. Indeed, these hospitals are used by many Venezuelans living outside the urban limits and service roughly 1,200,000 people. High quality autopsy evidence, therefore, suggests that the annual age-adjusted Alzheimer's disease mortality rate in this part of Venezuela is probably much less than 1 per 1 million population.<sup>18</sup> From a geographical viewpoint, Maracaibo is clearly the key to halting the worldwide Alzheimer's disease pandemic since it is a city where this form of dementia is virtually nonexistent.

In contrast to the dearth of Alzheimer's disease patients found in Maracaibo, the highest rates of this type of dementia appear to occur in parts of Norway. Excellent death certificate data is recorded in this country, with up to three contributory causes of death being coded, in addition to the major underlying cause. This data bank allowed Flaten<sup>19-20</sup> to calculate mean annual Norwegian age-adjusted dementia death rates per 100,000, for both males and females, for the 10 year period 1974 to 1983. That is, he worked out how many demented Norwegian people died in both gender groups over a decade. This calculation was completed for 193 Norwegian municipality aggregates, designed so that each statistical unit had a population of at least 10,000 inhabitants. From many autopsies it was known that approximately 60 to 75 percent of such Norwegians dying of dementia suffered from Alzheimer's disease. It is clear, then, that Flaten's illustrations of dementia<sup>21</sup> in Norway were dominated by the spatial distribution of Alzheimer's disease. Interestingly, although the maps illustrating male and female death rates with dementia were similar, both showed very marked regional variations. In both genders, dementia was a much more frequent cause of mortality along the south and southeastern coasts, while northern Norway and the inland areas of southern Norway generally experienced relatively low dementia death rates.

These differences in the spatial distribution of mortality were illustrated by the male annual age-adjusted dementia death rate per 100,000. This had a mean value of 25 for Norway as a whole, but varied at the municipal scale from approximately 5 to 74; in females the median rate was higher at 39, and ranged from 8 to 145. Given that autopsies had revealed that 60 to 75 percent of these Norwegian dementia cases had died with Alzheimer's disease, it seems that in the worst affected Norwegian municipalities, during the 10 year period 1974 to 1983, the median age-adjusted Alzheimer's mortality rates were between 44 to 55 per 100,000 for males and 87 to 109 per 100,000 for females. Clearly, within Norway, Alzheimer's disease-related mortality had been higher, by a factor of 15, in some regions than in others. If the higher rate municipalities in Norway are also compared with Maracaibo, it is apparent that death from Alzheimer's disease during roughly the same time period had been one thousand times more common in parts of Northern Europe than it had been in at least one region of Venezuela.

If the main causal variable(s) in Alzheimer's disease is genetic, that is an aberration that has been very widely dispersed in the human population, then age-adjusted mortality from this type of dementia would be relatively uniform. International, national, and regional patterns of death from Alzheimer's disease would show little variation, even though the individuals involved would appear to have been selected randomly. However, this is not the case. Everywhere that Alzheimer's disease mortality and incidence has been studied in detail geographically, including England and Wales,<sup>22</sup> Scotland,<sup>23</sup> Norway,<sup>24</sup> Canada,<sup>25</sup> the USA,<sup>26</sup> and China,<sup>37</sup> strong regional differences in incidence and/or mortality rates have been identified.

Alzheimer's disease does not occur uniformly. It is clear that the available evidence, from international to postal code scale,

strongly suggests that some areas unfortunately experience much higher Alzheimer's incidence and mortality rates than others. The rates of the two distribution extremes (Maracaibo and southeast coastal Norway) appear to differ by a factor of at least 1,000. That is, at every scale, Alzheimer's disease shows non-random geographical variation. This spatial distribution is the reverse of what would be expected if the preeminent risk factor(s) for this type of dementia were one or more widely dispersed, common, genetic aberrations. Simply put, while genetic differences probably play a role in sporadic Alzheimer's disease, they cannot be the major actors in this drama.

## **IMPACT OF MIGRATION: GENETIC COROLLARY TWO**

Further evidence that geography, not genetics, is the most significant player in Alzheimer's disease comes from migrant studies. If this type of dementia had a dominant genetic cause, migration by members of specific racial or ethnic groups should not result in any significant changes to either its incidence or age-adjusted death rate. This is because, in genetic illness, the causal variable is internal and migrates with the individual. Genes are definitely destiny. This type of relationship, however, is not seen in Alzheimer's disease. Graves and colleagues,<sup>28</sup> for example, in a research project conducted during the period 1992 to 1994, established the prevalence rates of dementia in general, and vascular dementia and Alzheimer's disease in particular, amongst Japanese Americans living in King County, Washington State who were 65 years of age or older. The initial baseline examination of this ethnic group included 1,985 people, 382 of whom received a diagnostic evaluation. As might be anticipated, the prevalence of dementia rose with age. Overall, the established prevalence rate for such Japanese American dementia was found to be 6.3 percent. Amongst those participants in the study aged from 85 to 89, 90 to 94, and 95

years and older, the dementia prevalences were 30, 50, and 74 percent respectively. For the same three groups, Alzheimer's disease prevalence rates reached 14, 36, and 58 percent. It was apparent from the data collected in this King County, Washington State study that Japanese Americans suffered much higher rates of dementia in general and Alzheimer's disease in particular than are found in similar aged populations living in Japan. Beyond this, the distribution of subtypes of dementia much more closely resembled that found in European and North American Caucasians than it did amongst elderly Japanese living in their homeland. Consequently, the occurrence of Alzheimer's disease was higher and the prevalence of vascular dementia lower in King County's Japanese Americans than might have been anticipated from available Japanese dementia data.

Similar results were reported by Hendrie and colleagues,<sup>29-30</sup> who have shown that African Americans develop Alzheimer's disease more frequently than West Africans. This research team conducted the Indianapolis-Ibadan Dementia Project, a longitudinal prospective population-based study designed to see if there were international differences in the prevalence of Alzheimer's disease and other forms of dementias in those of African descent. This project consisted of baseline surveys, conducted in both Indianapolis and Ibadan, during the period 1992 and 1993 and two subsequent waves of interviews and diagnoses, taking place 2 (1994-1995) and 5 (1997-1998) years later. The participants in this project were 2,459 Yoruba residents in Ibadan, Nigeria and 2,147 African American residents of Indianapolis, Indiana, all aged 65 or older. At the start of the project, none of those studied had dementia and all lived freely in their respective communities. To avoid any question of diagnostic differences or errors in diagnosis, identical methods were used in both countries by the same team of research workers. Nevertheless, they were able to show that African

Americans developed Alzheimer's disease at more than double the rate seen in Nigerian Yoruba of the same age. That is, the age-standardized annual incidence rates of Alzheimer's disease for African Americans were more than twice those of Nigerian Yoruba.<sup>31</sup>

Both the King County, Japanese survey and the Indianapolis-Ibadan Dementia Project clearly show that the types of dementia and, indeed, their frequency, appear strongly influenced by location. When ethnic groups move, migrant disease patterns soon seem to mirror those of new neighbouring ethnic groups rather than the current inhabitants of the region of origin. Such changes strongly suggest that the preeminent risk factor(s) in Alzheimer's disease and indeed vascular dementia cannot be genetic and are much more likely to be of either lifestyle and/or environmental origin.

## **SUMMARY**

The evidence presented in this chapter strongly suggests that there is no overriding, key genetic aberration in Alzheimer's disease. If there were, the global and regional incidence, prevalence, and mortality patterns for this type of dementia would be much more uniform than they are. Beyond this, migration would have little impact on the incidence and prevalence of Alzheimer's disease in identifiable ethnic groups, but clearly it has a significant influence. The only valid conclusion to be drawn from this epidemiological and geographical evidence appears to be that, although certain genetic aberrations may predispose to sporadic Alzheimer's disease, they must do so through their ability to promote the negative impact of specific lifestyle and/or environmental variables.

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*Some circumstantial evidence is very strong, as  
when you find a trout in the milk.*

Henry David Thoreau

## BIOCHEMICAL ABNORMALITIES

*What we call the future is the shadow which our past throws in front of us.*

Marcel Proust (1871-1922)

Every disease or disorder involves biochemical abnormalities. All pathogens cause such irregularities, and so too do toxins. Genetic aberrations inevitably result in biochemical quirks, and so does trauma. Deficiencies or excesses of vitamins, minerals, fats, proteins, and other nutrients interfere with, or correct, biochemical activity. Drugs, herbs, and supplements are intended to rectify biochemical imbalances, while even stress, meditation, and exercise directly impact on the body's biochemistry. Clearly, if we do not identify a disease's abnormal biochemistry we will never adequately explain its causes.

### GLUCOSE

Every bodily function from breathing, feeling, and thinking to walking, swimming, and running requires energy. One major fuel source for such energy is glucose, which is available from circulating blood and stored fuels, such as glycogen, in the liver. Glucose is the body's primary fuel source and is derived from the breakdown of sugars and starches contained in foods.<sup>1</sup> However, it is unable to pass directly through cell walls and must be "escorted" by the hormone insulin. This relationship is often called the "lock and key model," with insulin permitting

glucose access to cells by attaching itself to receptor sites on their walls. Once glucose gains access to such cells with the assistance of insulin, it is used as an energy source. It is not surprising then that type 1 diabetics, who typically lack adequate insulin, suffer from hyperglycemia, a condition characterized by abnormally high blood glucose levels.<sup>2</sup>

Diabetics are not the only ones who display glucose abnormalities. Several studies have shown that patients with mild and severe Alzheimer's disease have low levels of brain glucose metabolism. Alexander and coworkers, for example, used fluorodeoxyglucose (FDG) position emission tomography (PET) to study the brains of a group of Alzheimer's patients over a period of 1 year. Their results demonstrated that not only do those with this disorder have significantly lower than normal brain glucose metabolism, but that this declines as Alzheimer's disease progresses.

Such glucose abnormalities may occur many years before any signs of the disorder become apparent. Reiman and colleagues,<sup>4</sup> for example, identified abnormally low glucose metabolism in the brains of patients aged between 20 and 39, that is decades before the usual onset of any Alzheimer's symptoms. In their study, brain scans were taken of 12 such youthful patients who carried the APO E4 gene and 15 who did not. Results showed that those with this genetic characteristic already experienced abnormally low brain glucose metabolism.<sup>5-6</sup>

Nevertheless, the available evidence does not seem to show that a lack of glucose kills brain cells directly.<sup>7</sup> Under normal circumstances, brain cells are able to protect themselves against toxins, such as calcium homeostasis and aspartate. However, if they are glucose deficient this ability declines and they become much more prone to the destruction caused by such excitotoxins. Excitatory amino acids, including glutamate and

aspartate, normally exist in low concentrations in the brain without causing significant damage. However, if the brain becomes hypoglycemic, that is short of glucose, such toxins start to destroy brain cells, even at their normal levels. This may be what occurs in Alzheimer's disease.<sup>8-9</sup>

## **THE CHOLINERGIC SYSTEM**

Many of the cognitive deficits seen in Alzheimer's disease seem linked to problems in the cholinergic system. Choline acetyltransferase is reduced, for example, especially in the temporal cortex and the hippocampus.<sup>10</sup> In addition, Alzheimer's affected brains, again in their cortical and hippocampal areas, show a marked decrease in forebrain cholinergic neurons. Concentrations of cerebrospinal fluid acetylcholine are also depressed in Alzheimer's disease patients and are positively correlated with dementia scale test scores.<sup>11</sup> All this evidence, combined with studies that show that anticholinergic drugs cause a decline in memory, support the view that many of the cognitive deficits that occur in Alzheimer's disease patients are probably caused by cholinergic abnormalities.<sup>12</sup> Cholinergic deficiencies may also play a role in noncognitive problems, for example, in unwanted behaviours and in the deposition of toxic neuritic plaques that are characteristic of this form of dementia.

Choline, one of the B complex vitamins, is known to play a variety of important roles, such as maintaining cell membrane integrity and metabolizing lipids.<sup>14</sup> It is not surprising, therefore, that choline brain deficits cause serious side-effects. Indeed, it may be recalled that certain neurons, found at the base of the brain, known as the Nucleus Basalis of Meynert, appear to die in Alzheimer's disease, without any evidence of the interference of plaques or tangles.<sup>15</sup> Such neurons normally produce acetylcholine, a neurotransmitter that cannot

be created without choline. It is to be expected, therefore, that acetylcholine is deficient in the brains of Alzheimer's patients and that this abnormality is paralleled by memory decline.<sup>16</sup>

### **THE CATECHOLAMINERGIC SYSTEM: DOPAMINE, NOREPINEPHRINE, AND SEROTONIN**

Three of the main neurotransmitters of the nervous system – dopamine, norepinephrine, and serotonin – can be derived from the amino acid tyrosine. The enzyme tetrahydrobiopterin, required for the synthesis of these three neurotransmitters, is significantly depressed in the cerebrospinal fluid of patients suffering from Alzheimer's disease.<sup>17</sup> It is not surprising, therefore, that the brains of patients with this type of dementia contain less dopamine, norepinephrine, and serotonin than usual.<sup>18-19</sup> Several studies have demonstrated that the sub-normal production of these neurotransmitters appears to be linked to the death of dopamine receptors and noradrenergic and serotonergic neurons, in the cortex and elsewhere in the Alzheimer's brain. Joyce and coworkers,<sup>20</sup> for example, argued that the loss of the D2 receptor-enriched modules in the brains of Alzheimer's patients contributed to disturbances in information processing that may be responsible for cognitive and noncognitive impairments. Similarly, Palmer<sup>21</sup> has suggested that the absence of noradrenergic and serotonergic neurons probably contributes to the noncognitive impairments in behaviours seen in Alzheimer's patients.

### **THE GLUTAMATERGIC SYSTEM**

It is now generally agreed that glutamate is the major fast excitatory brain neurotransmitter. That is, it plays a key role in stimulating brain neurons. There are at least three different

types of glutamate receptors in the human brain and it appears that glutamate is as important a synaptic transmitter as acetylcholine. There is a profound reduction in glutamatergic neurotransmission in Alzheimer's disease that results from the loss of pyramidal neurons and cholinergic innervation.<sup>23</sup> This deficit is associated with significantly depressed plasma glutamate levels and abnormally low glutamine cerebrospinal fluid/plasma ratios.<sup>24</sup> Furthermore, there appears to be a strong correlation between behaviour and coping ability in Alzheimer's patients and cerebrospinal fluid glutamate levels, which provides clear evidence of a role for the disruption of amino acid metabolism in the disease.

## **PARATHYROID HORMONE AND CALCIUM**

It has been suggested often that some of the neurodegenerative changes occurring in Alzheimer's disease may be linked to depressed calcium homeostasis. Ferrier and coworkers,<sup>25</sup> for example, used radiocalcium to compare the absorption of calcium by Alzheimer's disease and multi-infarct dementia patients. They discovered that, although Alzheimer's disease patients appeared to have normal serum concentrations of parathyroid hormone and vitamin D metabolites, they were still less capable of absorbing calcium. This may account for the high prevalence of reduced bone mass in elderly women with Alzheimer's disease.<sup>26</sup> It may also account for the abnormally high brain adenylate cyclase activity found in such dementia patients.<sup>27</sup>

Adenylate cyclase is a catecholamine sensitive enzyme<sup>28</sup> that plays a significant role in parathyroid hormone secretion. Calcium inhibits adenylate cyclase activity, but magnesium promotes it, thereby stimulating the production of parathyroid hormone.<sup>29</sup> Indeed, Zimmerman and colleagues<sup>30</sup> have

suggested that the adenylyl cyclase catalytic mechanism involves two magnesium ions. While adenylyl cyclase activity declines in the non-demented elderly, no such reduction is seen in Alzheimer's patients, who typically show abnormally high brain adenylyl cyclase activity.<sup>31</sup> This may be a reflection of their calcium deficiency.

## **MAGNESIUM, ALUMINUM, AND IRON**

Numerous studies have uncovered the presence of elevated aluminum in brain tissue obtained from patients with Alzheimer's disease. For example, Pearl and Broady<sup>32-33</sup> used X-ray spectrometry to show aluminum accumulation in neurofibrillar tangle-bearing neurons. Subsequently, Glick<sup>34</sup> reanalysed Pearl and Broady's data to highlight the fact that Alzheimer's disease neurons also showed a significant lack of intracellular magnesium when compared to those of controls. This analysis appears to confirm the findings of Korf and coworkers,<sup>35</sup> who reported depletion of magnesium, potassium, and glutamic acid in the hippocampus of Alzheimer's patients, even though the magnesium level of the whole brain remained normal. Durlach's<sup>36</sup> conclusion was that magnesium depletion of the hippocampus represented an important pathogenic factor in Alzheimer's disease.

Neurofibrillar tangles are highly characteristic of the Alzheimer's disease brain. While they are largely composed of the protein tau, it is also well established that they contain not just aluminum, but also iron.<sup>37</sup> This appears to be because these two elements show phosphate-dependent binding with hyperphosphorylated tau. Interestingly, for the aggregation of hyperphosphorylated tau to occur and so form tangles, the iron involved must be oxidized, since reduced iron lacks this ability.<sup>38</sup>

There is also growing evidence that aluminum ions act synergistically with iron ions to increase free-radical damage.<sup>39</sup> The ingestion of aluminum by rats, for example, has been demonstrated to increase lipid peroxide formation by 142 percent in their brains and to stimulate iron-dependent peroxidation of liposomes, micelles, and red blood cells. The iron-binding and transporting protein transferrin is, in addition, the chief aluminum-binding protein of the plasma.<sup>40</sup> Once it has bound to transferrin, aluminum is able to enter cells, including those of the central nervous system, via transferrin receptors. In this way, aluminum and iron can both reach the brain.<sup>41</sup> This may be very significant since, as Sohler and coworkers<sup>42</sup> showed in a sample of 400 psychiatric outpatients in New Jersey, memory loss increased as blood aluminum levels rose.

## **TAU AND NEUROFIBRILLARY TANGLES**

The most obvious hallmarks of Alzheimer's disease are clusters of protein in the brain. These can occur both inside nerve cells and between cells. The clusters in the interior of cells are known as neurofibrillary tangles and they resemble pairs of threads that are wound around each other to form a helix. It is well established that these tangles are largely composed of a protein called tau. Tau is important because normally it binds with another protein, tubulin, which is used to form structures known as microtubules.<sup>43</sup> These microtubules are of great biological significance because they act like the pillars and girders of a building, giving shape and structure to cells. Such microtubules also provide pathways along which nutrients, other molecules and cellular components pass through cells.<sup>44</sup>

Protein phosphorylation is the primary control mechanism for the regulation of a wide variety of cellular processes, including cell division, protein synthesis, and neurotransmission.



Phosphorylation consists of the addition of a phosphate ( $\text{PO}_4$ ) group to a protein or to a small molecule.<sup>45</sup> Phosphorylation provides a very fast way of regulating proteins. If a protein, such as tau, is regulated by phosphorylation it is always present in “standby” mode. When an activating signal arrives, the protein is phosphorylated and then performs in the way intended. With the arrival of a deactivating signal, the protein again becomes dephosphorylated and ceases to work. As can be seen, phosphorylation and dephosphorylation act rather like a protein light switch that consists, in part, of a phosphate group.<sup>46</sup>

Tau is always present in cerebrospinal fluid. Sjögren and coworkers,<sup>47</sup> for example, have measured levels found in healthy adults, aged from 21 to 93 years, finding that tau typically increases with age. It is known, however, that the tau in the brains of Alzheimer’s patients is abnormal in that it is hyperphosphorylated, that is phosphorylated to excess. It has been corrupted by several extra molecules of phosphorus.<sup>49</sup> As a result, the tau malfunctions and becomes unable to support tubulin’s role in the production of microtubules, which, therefore, lack integrity and begin to twist. Communication and cell nourishment is compromised and eventually declines to zero. The neuron cannot be sustained and begins to wither. The cell membranes collapse and every part of the neuron disintegrates and with it synapses, each representing a memory fragment. How much of this process of the formation of neurofibrillary tangles and neuron destruction requires the presence of the iron and aluminum, previously described, is unclear.

## **BETA-AMYLOID PEPTIDE AND SENILE PLAQUES**

Unlike neurofibrillary tangles that occur inside neurons, deposits of amyloid protein gather in the spaces between nerve cells. Such plaques occur often and early in the development

of Alzheimer's disease and so researchers tried for many years to understand their biochemistry. In 1984, George G. Glenner of the University of California at San Diego found that their chief component was a peptide, that is a very short protein fragment, that consisted of 42 amino acids. This substance, the chief component of the plaques seen in the Alzheimer's disease brain, is now called beta-amyloid peptide.<sup>51</sup> It quickly was discovered to be formed from a more complex protein, the canning. This bigger protein is broken down in several different ways in the body. To illustrate, alpha- and gamma-secretase enzymes can cut it, giving rise to the three fragments which are not toxic. Alternatively, it can be cut by beta- and gamma-secretase. When this occurs, the process yields a harmless 40-amino-acid-long beta-amyloid peptide or a toxic 42-amino-acid peptide. It is the latter, of course, that builds up outside nerve cells to form the plaque seen in Alzheimer's disease brains.<sup>52</sup> In some cases, this accumulation occurs because the E<sub>4</sub> form of apolipoprotein is selectively removed from extracellular space instead of beta-amyloid peptide. As a consequence, the latter builds up to create plaques.<sup>53</sup> Unlike tau, the body's production of the 42-amino acid form of beta-amyloid, measured in cerebrospinal fluid, does not increase with age.<sup>54</sup> Indeed, levels of this peptide decrease in the cerebrospinal fluid of patients with Alzheimer's disease.<sup>55</sup> Interestingly, studies examining the role that cholesterol may play in plaque formation have shown that the 42-amino acid form of beta-amyloid builds up more easily in the brains of rabbits given tap water than it does if these animals drink distilled water.<sup>56</sup> Obviously, this suggests a water quality role in Alzheimer's disease.

The 42-amino acid form of beta-amyloid seems to damage the brain in various ways.<sup>57</sup> It appears, for example, to interfere with calcium regulation, to promote destructive free radicals, and to cause immune cells such as microglia to aggregate, a

process which leads to inflammation and to the exacerbation of previous injury.

Recent research has shown that the beta-amyloid of Alzheimer's neurofibrillary tangles consists of more than just protein. It is a metalloprotein, housing atoms of the metals copper, zinc, and iron within its tangles.<sup>58-59</sup> Each of these metals can react with oxygen but copper promotes free radical damage while zinc is generally considered a protective antioxidant. Interestingly, copper chelators that can attach themselves to this element and eliminate it for the body, have been shown to greatly reduce amyloid plaques in the brains of living mice.<sup>60</sup> Clinical trials are in progress to determine whether the same is true of humans. A study at the Sanders-Brown Center on Aging in Louisville, Kentucky also has found that at low levels zinc provides protection against amyloid plaques, while at elevated levels it promotes their formation.<sup>61</sup>

## **OTHER PROTEINS**

Recent research has shown that other proteins also appear to play roles in Alzheimer's disease. To illustrate, endoplasmic-reticulum associated binding protein (ERAB) can combine with beta amyloid which, as a result, attracts more beta amyloid protein into the cell.<sup>62</sup> Elevated endoplasmic-reticulum associated binding protein also increases beta amyloid's nerve-destructive power. In addition, 100 kD AMY protein is capable of forming plaques that are very similar to those composed of beta amyloid. Beyond this, the protein prostate apoptosis response-4 can encourage nerve cells to self-destruct.<sup>63</sup>

## SUMMARY

It is apparent from this short review that Alzheimer's patients display a wide variety of biochemical abnormalities. These include low brain glucose metabolism and the malfunctioning of neurotransmitters such as acetylcholine, dopamine, norepinephrine, serotonin and glutamate. Also present in this form of dementia are deficiencies of both brain calcium and magnesium and excess of iron and aluminum. Beyond this, disruption is caused by two abnormal proteins, hyperphosphorylated tau and the 42-amino acid form of beta-amyloid peptide.

It is possible, but unlikely, that each one, or most, of the biochemical abnormalities just described in Alzheimer's disease is linked to its own distinct genetic aberration or environmental trigger. It is possible also that these may be part of a chain of cause and effect. If this is the case, a single genetic aberration or environmental toxin may result in one initial biochemical abnormality. This in turn may trigger a second and so on, eventually pushing over dominoes known as dopamine, serotonin, calcium, and hyperphosphorylated tau to name but a few. If Alzheimer's disease is caused by such a reaction, its key is the identification of where each of these biochemical dominoes occur in the causal chain. If we can prevent the first domino from falling, we can stop the collapse of all and so prevent the disorder.

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## OTHER RISKS, FURTHER HAZARDS

*I can't understand why people are frightened of new ideas. I'm frightened of the old ones.*

John Cage (1912 - 1992)

### LONGITUDINAL STUDIES

One lengthy, painstaking, and costly way of attempting to identify other risk factors for Alzheimer's disease is the longitudinal study.<sup>1</sup> These studies often involve enrolling thousands of people in projects that may last for decades. Volunteers are given medical examinations at regular intervals, perhaps once or twice a year, and are repeatedly questioned about their lifestyles, occupations, hobbies, and other topics that might be related to disease development. They may be monitored like this anywhere from a couple of years to half a century, or until their deaths. In some longitudinal studies, the bodies of volunteers are eventually subjected to autopsy.

Numerous longitudinal studies of memory decline have been in progress for two or three decades and are now beginning to identify risk factors that may be related to Alzheimer's disease. Some of these variables, such as high blood pressure, elevated cholesterol and homocysteine levels, obesity, poor diet, smoking, depression, head trauma, chronic stress, osteoporosis, and diabetes mellitus, can be controlled. In contrast, other such

variables, including having the APO E4 gene, or family members with Alzheimer's disease, or lack of childhood education or aging, can no longer be influenced.<sup>2</sup>

## Hypertension

The Honolulu Heart Program/Honolulu-Asia Aging Study was one such longitudinal project. As described in two articles published in the *Neurobiology of Aging*,<sup>3,4</sup> this involved measuring the blood pressure, in 1965, 1968, and 1971, of 4,678 Japanese-American males who had been born between 1900 and 1919 and who resided in Hawaii. Some 25 years later, 3,734 of these volunteers, who could still be traced, had their blood pressures remeasured and in addition were given cognitive tests. It was discovered that those subjects who, 25 years earlier, had suffered from untreated hypertension (systolic blood pressure greater than 160 mm Hg) were 4.8 times more likely to be demented than those whose pressure readings had been normal.<sup>5</sup>

By the year 2000, the brains of 243 of these volunteers had been autopsied. A direct relationship was identified between elevated diastolic blood pressure (95 mm Hg or greater) and both atrophy (shrinkage) of the brain and the presence in it of neuritic plaques and neurofibrillary tangles. That is, high blood pressure in mid-life was found to help predict the development of Alzheimer's disease in old age. A similar longitudinal project, the Systolic Hypertension in Europe (Syst-Eur) Study has demonstrated further that blood pressure-lowering therapy, using long-acting dihydropyridine, protected against dementia in those with this form of hypertension.<sup>6</sup> The available evidence, recently summarized by Fotuhi,<sup>7</sup> therefore, strongly suggests that hypertension, especially if it goes untreated, increases the probability of subsequently developing Alzheimer's disease.

## Cholesterol

Whether or not high cholesterol is a significant risk factor in Alzheimer's disease is still being debated. Experimental evidence, however, suggests that cholesterol promotes the formation of amyloid plaques.<sup>8</sup> Sparks, for example, was able to increase or decrease the amyloid brain load in rabbits by providing them with cholesterol-enhanced, or depleted, diets. This relationship was confirmed in experiments using genetically engineered mice.<sup>9</sup> Similarly, Simons and coworkers<sup>10</sup> showed that, in the test tube, cholesterol depletion with drugs inhibits the formation of beta-amyloid in the hippocampal neurons of fetal rats.

Does a similar cholesterol-amyloid plaque relationship occur in humans? There is evidence from several longitudinal studies that suggests that it does. In Scandinavia,<sup>11</sup> the blood pressures and cholesterol levels of 1,449 volunteers were followed for more than 20 years. Those with high cholesterol levels (more than 250 mg/decilitre) in mid-life were found to be 2.2 times as likely to develop Alzheimer's disease as they aged than were those with normal mid-life cholesterol levels. This probability figure rose to 3.5 in individuals with both high cholesterol and elevated blood pressure. Similarly, for 4 years, Yaffe<sup>12</sup> and coworkers monitored total cholesterol, LDL (low density lipoproteins), and HDL (high density lipoproteins) in 1,037 post menopausal women who suffered from heart disease and were part of the Heart and Estrogen/Progestin Replacement Study. Those with the highest total cholesterol levels were found to be 1.76 times more likely to develop mild cognitive impairment than those with the lowest cholesterol levels. Interestingly, it appeared to be LDL, not HDL, that were associated with this impairment. Similarly, Kawas and Corrada<sup>13</sup> found a link between a high ratio of LDL to HDL and dementia in the data collected during a Baltimore longitudinal study of aging.

It is not surprising, therefore, that evidence is growing that cholesterol-lowering medications, such as statins, may reduce the risk of developing Alzheimer's disease. Using data from the British General Practice Research Database, Drachman and coworkers<sup>14</sup> compared 25,000 people with normal lipid values, 25,000 with elevated levels who were on medication to lower these, and 25,000 with high values who were not on medication. Over 6 years, 284 of the patients were diagnosed with dementia. It was found that those taking statins had a 70 percent lower risk of becoming demented. Similarly, Wolozin and colleagues<sup>15</sup> studied the records of 56,000 patients treated in military hospitals in the USA and discovered that those on statins had a 60 to 73 percent lower risk of developing Alzheimer's disease than patients who took other medications to reduce their blood pressures. Beyond this, Green and coworkers<sup>16</sup> studied 2,581 patients at 15 medical centres in Canada, the USA, and Germany where they found that, regardless of genetic risk or ethnicity, those who took statins for at least 6 months reduced the risk of developing Alzheimer's disease by 79 percent.

There is, however, at least one major study that denies this cholesterol-amyloid plaque-Alzheimer's disease association. In 2003, Tan and colleagues<sup>17</sup> examined this possible link using data from the Framingham Study, one of the largest and most comprehensive longitudinal projects ever undertaken. Their research involved a subgroup of Framingham Study volunteers who had been evaluated biannually for cardiovascular risk factors since 1950. Members of this subgroup were alive and free of both stroke and dementia when re-examined during 1988 and 1989 and had also undergone apolipoprotein E (APO E) genotyping. Alzheimer's disease subsequently developed in 77 of these 1,027 volunteers during the time period 1992 to 2000. However, no link was found between average cholesterol level (measured 15 times) or total cholesterol at examination number 20 and the future risk of developing Alzheimer's disease.

## Homocysteine

The essential amino acid methionine is the indirect source of homocysteine. As methionine is metabolized it produces homocysteine before either recycling it to methionine, or creating a final breakdown product, cystathionine. The former step requires vitamin B<sub>12</sub> and folate and the latter needs vitamin B<sub>6</sub>.<sup>18</sup> Inadequacies of these three key vitamins can slow homocysteine metabolism and allow abnormal levels of it to build up, creating a condition known as homocysteinemia. This has been associated with strokes, atherosclerosis, and cardiovascular disease. It is well known also that the oxidation product of homocysteine, homocysteic acid, exerts potent excitatory effects.<sup>19</sup> Beyond the elevation of homocysteine caused by deficiencies of vitamins B<sub>6</sub>, B<sub>12</sub>, and folate, it is known also that certain genetic aberrations can promote excesses of this amino acid. To illustrate, methylenetetrahydrofolate reductase (MTHFR) is involved in the remethylation of homocysteine to methionine. The gene for MTHFR is located on chromosome 1. Rare allelic variants can cause severe methylenetetrahydrofolate reductase deficiencies resulting in homocystinuria.<sup>20</sup> It would seem, therefore, that some people have above normal blood levels of homocysteine because of one or more of vitamin B<sub>6</sub>, vitamin B<sub>12</sub>, or folate deficiencies, while others have inherited a genetic aberration that predisposes them to this condition.

In 2002, Seshadri and coworkers<sup>21</sup> described the results of a longitudinal homocysteine and dementia study, conducted with the aid of 1,092 elderly people living in Framingham, near Boston. The subjects in this study were non-demented men and women with an average age of 76. Over the 8 years for which their health was followed, 111 developed dementia. It was found that those with high plasma homocysteine levels, when first measured, were twice as likely to have developed

Alzheimer's disease than those with normal levels, that is with less than 14 micromoles per litre. For each five-point increase in the levels of plasma homocysteine, a 40 percent increase in the risk of Alzheimer's disease occurred. A study of community-dwelling elderly Latinos in the Sacramento area has since confirmed that plasma homocysteine is an independent predictor of cognitive function.<sup>22</sup>

## Diet

Animal studies have shown that diets rich in antioxidants can improve memory. The evidence seems best for spinach<sup>23</sup> and blueberries,<sup>24</sup> both of which have been shown to alter rat behaviour and make measurable differences in their memory performances. Curcumin, a component of curry spice, is also a strong antioxidant which, in both the test tube and in animal models of Alzheimer's disease appears capable of reducing amyloid protein toxicity.<sup>25-26</sup> Interestingly, curry is much more widely used in India than in the USA and Alzheimer's disease is far less common in the elderly of the former country than of the latter.

Another herb that seems to improve memory and that may be useful in reducing the risk of Alzheimer's disease is Spanish Sage (*Salvia lavandulaefolia*). As early as 1597, the herbalist John Gerard wrote that sage "is singularly good for the heart and brain and quickeneth the nerves and memory." Similarly, Nicholas Culpeper writing in 1652 claimed that sage "also heals the memory, warming and quickening the senses."<sup>28</sup> Support for these claims has been provided by Tildesley and colleagues<sup>29</sup> of the Division of Psychology, Northumbria University, who tested the effects of sage and a placebo on the memories of 44 healthy young adults. Volunteers in this study were given tests at intervals to establish immediate word recall. Those who took sage oil consistently outperformed those who received

placebos. As has been described earlier, Alzheimer's disease patients are typically deficient in the chemical messenger acetylcholine. Sage has been found to inhibit the enzyme acetylcholinesterase which breaks down acetylcholine and so presumably increases levels of this neurotransmitter in the brain, improving memory.<sup>30</sup>

Two recent longitudinal studies have shown also that vitamin E reduces the risk of developing Alzheimer's disease. This vitamin, of course, is also a strong antioxidant. In one such project, Breteler and colleagues<sup>31</sup> interviewed 5,395 Dutch volunteers, aged 55 or more, and gathered details of their diets, smoking habits, and antioxidant supplement use. From available food charts, these researchers then estimated the participants' normal daily vitamin intake. After 6 years, 146 of these volunteers had developed Alzheimer's disease. It was found that this form of dementia occurred most often in those who consumed the lowest levels of vitamin E. In contrast, volunteers who ate a diet that contained the highest amounts of this antioxidant were 43 percent less likely to have developed this form of dementia. Similarly, Morris and coworkers<sup>32</sup> conducted a further longitudinal study in Chicago, and monitored 815 people, aged 65 or older, for 4 years. Those who ate a diet that contained the highest levels of vitamin E had 70 percent less chance of developing Alzheimer's disease than who consumed the lowest levels. The Dutch longitudinal study also suggested that those with high intakes of vitamin C also were less likely to develop Alzheimer's disease.<sup>33</sup>

Fish consumption also seems to decrease the possibility of developing this form of dementia.<sup>34-36</sup> This could be because of the protection that is provided by the high levels of omega 3 polyunsaturated fatty acids that are present in fish. This association appears to have been first pointed out by Grant,<sup>37</sup> but it has been confirmed numerous times since then, most



notably by Barberger-Gateau and colleagues,<sup>38</sup> who studied diet and the development of dementia amongst 1,674 elderly people, residing at home, in southwestern France. Three follow-up visits, made over a 7 year period, determined which of the volunteers were beginning to suffer memory loss. This longitudinal study established that eating fish at least once a week appeared to provide such elderly volunteers with a one-third reduction in the risk of developing dementia, during the 7 years of the study. A similar project, involving USA elderly, also confirmed that those who ate fish at least once a week were 60 percent less likely to develop Alzheimer's disease, during a 2 to 3 year follow-up period, than those who rarely or never ate it.<sup>39</sup>

In an interesting study,<sup>40</sup> 1,600 Italians over the age of 70 were asked what they ate regularly. Once this information had been collected, they then were subjected to neurological tests of language skills, memory, and attention. Their reported diets were then classified on a scale of 1 to 7, with the latter considered the healthiest, being low in fat and cholesterol but elevated in fibre, polyunsaturated omega-3 oils, nuts, fruits, and vegetables. Results suggested a close link between diet and cognitive impairment since those who ate the worst diets proved to be three times as likely to have scored poorly on their cognitive tests than those who consumed the best.

Beyond this, Wang and coworkers<sup>41</sup> studied the serum vitamin B<sub>12</sub> and folate levels in 370 non-demented Swedish elderly. After 3 years it became apparent that those with the lowest initial serum levels of either, or both, of these vitamins were twice as likely to develop Alzheimer's disease.

Clearly, there appear to be links between vitamin B<sub>12</sub>, folate, and antioxidant use, and other indicators of dietary quality, and the development of Alzheimer's disease. This association

may be stronger in women. Gustafson and colleagues,<sup>42</sup> for example, followed the changes in health of 392 non-demented Swedish adults from age 70 to 88, and discovered that for every 1.0 increase in body mass index (BMI) at age 70, women were 36 percent more likely to develop Alzheimer's disease by the time they reached 88. This association between obesity and Alzheimer's disease did not occur in males.

## Smoking

There is no doubt that smoking is a very dangerous habit that is thought to have killed some 200 million people during the 20th century. It has been linked to approximately 50 diseases, but whether Alzheimer's disease is one of them is still the subject of heated debate. On one side of the issue are those such as Lee,<sup>43</sup> and supporters in the Smokers' Rights Action Group.<sup>44</sup> The latter, for example, claim that in the USA non-smokers are more prone to develop Alzheimer's disease and as a result suffer 73,000 excess cases causing \$17.5 billion in unnecessary costs. Set against this position, for example, are Doll, Peto, and colleagues<sup>45</sup> from the Clinical Trial Services Unit and Epidemiological Studies Unit, Radcliffe Infirmary, Oxford and Wang and coworkers<sup>46</sup> of the Stockholm Gerontology Research Centre, who believe that smoking is not protective against Alzheimer's disease and, indeed, may promote it. Naturally, this position has the support of Action on Smoking and Health (ASH),<sup>47</sup> a 31-year-old legal-action antismoking and nonsmokers' rights organization.

In 1993, Lee<sup>48</sup> conducted a meta-analysis based on all of the data available at that time contained in English language case-control studies in which smoking had been investigated as a possible risk factor in Alzheimer's disease. His study combined data from 19 research publications which included 1,691 cases, most of whom had been patients in Veteran's hospitals.

Ten of these original research projects had been conducted in the USA, six in Europe, and one each in Japan, Colombia, and Australia. Lee's meta-analysis suggested that there was a highly statistically significant ( $p < 0.001$ ) negative association between ever having smoked and Alzheimer's disease. Smokers had only a 0.64 relative risk (RR) of developing this form of dementia. Lee concluded that his analysis supported the view that nicotine was protective against Alzheimer's disease and smokers, therefore, were less likely to develop it.

In 2002, Almeida and coworkers<sup>49</sup> from the University of Western Australia published the results of a further meta-analysis of the smoking-Alzheimer's relationship. This was based on 21 case-control studies that had been reported on between 1955 and 2000. They concluded that:

*... the results reported in these meta-analyses show that the direction of the association between smoking and AD [Alzheimer's disease] remains unclear. Previous claims that smoking reduces the risk of AD can no longer be supported. In fact, the results of recent cohort studies suggest that a history of smoking is associated with an increased incidence of AD – these findings are particularly robust for subjects who were current smokers at the time of enrolment. One obvious limitation, however, is that the number of cohort studies ( $n=8$ ) and incident cases available for analysis ( $n=1076$ ) is still too small to be used reliably as evidence that smoking increases the risk of AD. It is our view that this issue can only be addressed properly with a large cohort study designed to investigate the effects of smoking on cognitive decline and risk of AD – if its results confirm the trend observed by recent studies... then smoking prevention and cessation should become public health priorities in the fight against AD.*

At least two longitudinal studies have suggested that smoking does indeed promote, rather than protect against, Alzheimer's

disease. The first of these followed 6,870 men and women aged 55 and over, living in a suburb of Rotterdam, The Netherlands. None of them had Alzheimer's disease before the study, conducted by faculty at the Erasmus University Medical School, began.<sup>50</sup> Over a 2-year period, any of these 6,870 individuals who appeared to show early signs of dementia were assessed and, if possible, given brain scans. As a consequence, 105 were diagnosed with Alzheimer's disease. It was established that those volunteers who smoked were 2.3 times more likely to develop this form of dementia than those who had never done so. Interestingly, however, it was found that smoking did not increase the risk of developing Alzheimer's disease in those who carried the APO E4 gene, which has been linked to this form of dementia in the general population. Indeed, one of the researchers involved, Dr. Monique Breteler,<sup>51</sup> is quoted as saying "It seems that if you have the gene, you're better off if you smoke."

In 2000, the results of a second longitudinal study, conducted by Doll and coworkers<sup>52</sup> of Radcliffe Infirmary Oxford, was released. This was based on observations of more than 34,000 British doctors whose smoking habits had been recorded every 6 to 12 years since 1951. By the end of 1998, over 24,000 of these doctors were dead and dementia had been reported on the death certificates of 483 of them. From this available data these researchers argued that:

*Among 473 whose smoking habits were recorded at least 10 years before their death, when they would not have been influenced by the start of the disease, the prevalence of both Alzheimer's disease (the predominant cause) and of other dementias was similar in both smokers and non-smokers. If anything, persistent smoking may increase rather than decrease the age specific onset rate of dementia, conclude the authors.*

*The previous suggestions that smoking might be protective, say the authors, came from studies that were flawed because they were too small, or had relied on information about smoking habits from people other than the sufferers themselves.*

## **Depression**

As part of the ongoing Religious Orders Study,<sup>53</sup> in which researchers have been evaluating memory skills and the onset of Alzheimer's disease, more than 650 older nuns, priests, and brothers were given annual neurologic and memory examinations for 7 years. The results indicated that those participants who showed the greatest number of symptoms of depression at the beginning of the study were more likely to develop Alzheimer's disease as it progressed. If they did, their cognitive decline was faster than usual.

Given the prognosis for the disorder, it is hardly surprising that clinically significant depression occurs in some 20 to 40 percent of those diagnosed with Alzheimer's disease.<sup>54</sup> However, the Religious Orders Study<sup>55</sup> results suggest that the link between depression and this form of dementia goes deeper than that. In 2003, researchers from the Boston University School of Medicine<sup>56</sup> described results from the MIRAGE (Multi-Institutional Research in Alzheimer's Genetic Epidemiology) Study obtained by examining nearly 2,000 Alzheimer's patients and a matching number of their unaffected relatives. It was discovered that Alzheimer's disease was more likely to develop in both men and women who had displayed symptoms of depression within 1 year of onset of their dementia. However, those exhibiting depression several years earlier were still at increased risk of developing Alzheimer's disease. Even those suffering from depression 25 years previously were at slightly increased risk for this form of dementia.

## Head Trauma

Controversy continues over whether traumatic brain injury increases the probability of developing Alzheimer's disease.<sup>57</sup> Launer and coworkers<sup>58</sup> sought to answer this question by performing a pooled analysis of four European population-based prospective studies of individuals aged 65 years and older. These data included 528 incident dementia patients and 28,768 person-years of follow-up. Their analysis established that a history of head trauma with unconsciousness did not significantly increase the risk of subsequent Alzheimer's disease. Similarly, Nemetz and colleagues<sup>59</sup> followed up the medical histories of 1,283 traumatic brain injury cases that had occurred in Olmsted County, Minnesota, from 1935 to 1984. Thirty-one of these trauma patients subsequently developed Alzheimer's disease, a number similar to that normally expected in individuals without head injuries. However, the data clearly indicates that such head trauma had reduced the time-of-onset of Alzheimer's disease by about 8 years amongst persons at risk for developing it. That is, head trauma does not appear to increase the probability of developing Alzheimer's disease in the general population; however, those prone to it tend to suffer from it earlier than normally expected.

Why this happens is a question that appears to have been answered by Nicoll and coworkers.<sup>60</sup> These researchers have shown that the deposition of beta-amyloid in the brain had been promoted by head trauma, in approximately one third of individuals who died shortly afterwards from severe injury. The probability of deposition of such beta-amyloid, following trauma, is greater than would be anticipated statistically in individuals with the apolipoprotein E-epsilon 4 allele, that is the allele that has been linked to late-onset Alzheimer's disease. In short, in individuals with this genotype, severe head trauma often appears to initiate beta-amyloid deposition. Not

surprisingly, if they survive the trauma, such deposition reduces the time-of-onset of sporadic Alzheimer's disease in those genetically prone to it since, of course, beta-amyloid is the major constituent of neuritic plaques. This sounds like a clever and simple explanation of why there may be a head trauma-Alzheimer's disease link but it has been questioned by Mehta and coworkers<sup>61</sup> from Erasmus University Medical School in Rotterdam. They studied 6,645 people, aged 55 years or older, who had suffered mild head trauma with loss of consciousness and reported that it was not a risk factor for dementia or Alzheimer's disease in the elderly, nor did it promote the latter disorder in those with the APO E genotype. Clearly, the issue is still debatable although it may be that the head trauma must be severe before it promotes early onset of Alzheimer's disease.

### **Chronic Stress**

Investigators from Rush University Medical Center in Chicago have been taking part in the previously described Religious Orders Study evaluating aging in Catholic nuns, priests, and brothers.<sup>62-63</sup> As part of this research project nearly 800 participants about 75 years of age were evaluated for some 5 years. To assess their propensity to stress, they were questioned about worrying and feelings of being tense or jittery. During this study, 140 of these volunteers developed Alzheimer's disease. The collected data established that those in the 90th stress percentile were twice as likely to develop this form of dementia as those in the 10th percentile. Simply put, worriers were twice as likely to develop Alzheimer's disease as were more "laid back" individuals. The study also established that stress level was related to the rate of decline in episodic memory. Worriers, for example, were least capable of remembering word lists. This association between chronic stress and the risk of developing Alzheimer's disease remained even after controlling for factors such as depression and cognitive activity level.

## **Osteoporosis**

A recent longitudinal study followed 987 men and women with an average age of 76 years for a further 13 years.<sup>64</sup> Its aim was to examine possible links between bone mass and dementia. Interestingly, those women with the lowest bone mass measurements at the beginning of this study proved twice as likely to subsequently develop dementia as those with the densest, strongest bones. This relationship did not occur in men, suggesting that it may be linked to declining estrogen levels.<sup>65</sup>

## **Diabetes Mellitus**

Evidence from the previously described Religious Order Study also suggests that diabetes is associated with both a higher likelihood of developing Alzheimer's disease and a greater rate of decline in perceptual speed.<sup>66</sup> This risk is independent of a history of stroke and whether or not an individual has the APO E4 genotype. These conclusions were based on evidence from 869 older volunteers, none of whom had dementia when the study began. Those individuals were evaluated annually for up to 8 years in order to determine whether they were developing Alzheimer's disease or other forms of dementia. Cognitive function testing was also carried out. Amongst these volunteers were 125 (14.4%) who had diabetes. They were examined regularly for an average of 5.1 years. It was determined that such Catholic volunteers with diabetes had a 73 percent higher chance of developing Alzheimer's disease than controls, even after the impacts of age, gender, and education had been accounted for.

Similarly, Luchsinger and coworkers<sup>67</sup> investigated the impact of diabetes mellitus on the incidence of Alzheimer's disease in American Blacks and Hispanics. In a sample of 1,262 elderly subjects, followed for an average of 4.3 years, Alzheimer's



disease had an adjusted relative risk of 1.3 for those with diabetes as compared with those without it. These data were consistent with the belief that there is a modest relationship between diabetes and Alzheimer's disease.

## **Childhood Education**

There is considerable evidence from a variety of sources that those with relatively poor childhood education are more likely to suffer from Alzheimer's disease as they age. De Ronchi and coworkers<sup>68</sup> at the University of Bologna studied 495 elderly people of high to middle socioeconomic class. Those without education were 4.7 times more likely (after adjustment for age, gender, and occupation) to show signs of dementia than those with some formal education when young. This relationship was especially obvious amongst the youngest members of the study, aged 61 to 69 years, where the relative risk of dementia associated with no education was an amazing 139.5. Interestingly, this figure decreased with age. De Ronchi and colleagues concluded that early childhood education was critical in reducing the probability of developing Alzheimer's disease later in life.

Support for this view came from Hall and associates<sup>69</sup> of the Indiana University School of Medicine who studied links between Alzheimer's disease and the level of education and location of childhood residence in 2,212 African Americans, 65 years or older, living in Indianapolis. They concluded that rural residence combined with 6 or less years of education was linked to a higher risk of developing Alzheimer's disease amongst members of their sample. Mocerri and colleagues,<sup>70</sup> who conducted a case-control study in Seattle with 393 Alzheimer's patients and 379 controls for comparison also confirmed an early-life childhood and adolescent environment link to Alzheimer's disease risk. Similar results were reported from Finland by Kaplan and coworkers.<sup>71</sup>

## Aging

If, as has been previously argued, the preeminent risk factor in sporadic Alzheimer's disease is not genetic, then what is it?<sup>72</sup> Clearly, there must be other crucial causal variables(s) driving the dementia pandemic. The most obvious of these is simply the process of growing older. Unfortunately, short of deliberately increasing the mortality rate, an alternative that is promoted by right to die organizations such as *The Hemlock Society*,<sup>73</sup> there is little that can be done to halt the impact of an aging population on the incidence of Alzheimer's disease, until society is willing to accept the true cause of this form of dementia.

The evidence that the incidence and prevalence of Alzheimer's disease increases with aging is overwhelming. In the USA, the prevalence of severe dementia (much of it Alzheimer's disease), occurring amongst those aged 65 to 74 is roughly 1 percent, compared to 25 percent for those over 84.<sup>74</sup> There is a disputed suggestion that the risk of developing dementia may decline after age 84 is reached,<sup>75</sup> but this hypothesis appears to be in conflict with the results of detailed surveys of the elderly.<sup>76</sup> Evans and coworkers,<sup>77</sup> for example, found that in San Marino, an urban working class community of some 32,000 inhabitants, an estimated 10.3 percent of the population aged over 65 had probable Alzheimer's disease. The prevalence of this disorder increased steadily with aging, from 3.0 percent at age 65 to 74 years to 18.7 percent for those aged 75 to 84. This trend continued so that 47.2 percent of those 85 years or older were diagnosed as suffering from probable Alzheimer's disease. This age-related increase in dementia was identified again in San Marino.<sup>78</sup> At age 67 only 1.8 percent of the population suffered from it, a figure that rose to 25.0 percent in those 87 years of age. The general situation was summarized by Jorm, Korten, and Henderson<sup>79</sup> who, after a survey of the

international literature, concluded that dementia prevalence rates reflected the age of the sample population, doubling every 5.1 years.

## **SUMMARY**

The evidence presented in this chapter, drawn mainly from longitudinal and case-control studies, clearly shows that certain health conditions increase the future likelihood of developing Alzheimer's disease. These include high blood pressure, elevated cholesterol and homocysteine, chronic stress, head trauma, depression, osteoporosis, and diabetes mellitus. What is less obvious is whether the genetic aberration(s) that predispose to Alzheimer's disease and/or the environmental factors that trigger these genotypes also cause such health states, or whether they themselves promote dementia directly. Does high blood pressure, for example, increase the risk of Alzheimer's disease directly or do the variable(s) that cause hypertension also promote this form of dementia?

Other factors that appear implicated in a greater risk of developing Alzheimer's disease include poor diet and obesity, and a lack of childhood education. Aging, of course, is also a very key variable, while the jury is still out on the significance of smoking in the etiology of Alzheimer's disease.

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*When the vet had finished his visit we had the opportunity to chat. I asked him what was, in his opinion, the cause of these many cases of grass tetany on his clients farms. He replied that he did not know. I then put to him the question: "Do you know to what extent your client employs potash on his grassland?" The reply has remained fixed in my memory: "This question concerns the farmer. My role is to care for sick animals and cure them."*

*It think that it is this idea which should not dominate veterinary and medical science in the future. It is not merely a question of healing the animal or Man stricken by disease, it is necessary to heal the soil so as not to have to heal the animal or Man.*

*We concentrate our efforts on the results and neglect the causes.*

A. Voisin, *Soil, Grass and Cancer*

*The relentless American focus on health sustains popular magazines and fills the airwaves with health claims for cereals, vitamins, pills, and exercise equipment. We are told how to eat the right foods and avoid the wrong ones, practise safe sex, work out properly, get regular check-ups, think healthy thoughts, and accept responsibility for our own destinies. But no matter how diligently we take care of ourselves, no matter how often we say no to unsafe sex or dangerous drugs or choose the salad instead of the hamburger, we cannot control the influences of the world around us. Where you live and work, what you eat and drink and breathe, what happened to you just before birth – all those things play critical roles in determining your prospects for health. But when illness is not a matter of personal prevention, scientists and media alike become strangely reticent.*

Devra Davis (2002)<sup>1</sup>

In the early 1980s, I was dedicated to searching for the causes of cancer.<sup>2</sup> This illness does not strike at random. *Patterns in Cancer Mortality in the United States: 1950-1967*<sup>3</sup> clearly revealed very significant differences in the geographical distribution of death from various types of malignant neoplasms. This volume, Monograph 33 of the United States National Cancer Institute, contains age adjusted death rates per 100,000 population, for 65 specific or subgroups of cancers, and for the disease as a whole. In total, it provides data on the type of cancer which caused the deaths of more than 4,600,000 people during the

period 1950 through 1967. These data had been taken from death certificates and mapped at the state scale. Correlation of these 66 cancer groups with each other allowed the identification of those malignant neoplasms that have the same environmental triggers and those that do not. Breast cancer, for example, tends to be elevated where cancers of the ovary and digestive tract are also common, but shows a marked negative relationship with both skin cancer and melanoma.<sup>4</sup>

I developed this technique further in a later book, *Health, Disease and the Environment*.<sup>5</sup> In this volume, and in subsequent papers, I correlated (that is compared statistically) maps of the incidence, prevalence, or death rates from 74 different health problems, ranging from SIDS, diabetes mellitus, and multiple sclerosis to cancer, Parkinson's disease, and schizophrenia. Again, it was obvious that some of these illnesses tended to occur at high levels together in the same populations, while others never did. This suggested to me that a variety of environmental triggers were involved, some of which probably either helped cause, or prevent, more than one illness.

To try to identify what these triggers were, I developed a computer database containing information on the spatial distributions, in the USA, of 219 natural or man-made environmental substances<sup>6</sup> ranging from sunlight and precipitation through road salt use, dieldrin, lindane, and arsenic in surface waters to hay, potatoes, tobacco, and cotton production. Extensive data on soil geochemistry also were included in this database. These 219 potential triggers were then correlated with the spatial patterns of all of the 66 cancers or groups of cancers to identify which had either very similar, or very different, distributions. The thousands of resulting correlations were suggestive of links between many cancers and soils containing lower than normal levels of calcium and selenium. Death rates from such malignant neoplasms in the USA were also very high where

road salt was used extensively and soil mercury levels were elevated. Although I have read and published widely on cancer since 1986, when this original work was published, nothing has made me alter my opinion on this topic. Rather, the evidence is now much stronger that these triggers are involved in the etiology of cancer.

I have since used this environmental database to explore for triggers in numerous other diseases and disorders, identifying, for example, what I believe to be a lack of selenium in myocardial infarction<sup>7</sup> and iodine deficiencies in Sudden Infant Death Syndrome (SIDS),<sup>8</sup> amyotrophic lateral sclerosis (ALS), multiple sclerosis (MS), and Parkinson's disease.<sup>9</sup>

From this research it became obvious that it is unrealistic to study the impacts of single environmental variables on human health.<sup>6</sup> Many such factors interact either antagonistically or synergistically, so that there is an increase or decrease in health impacts when individuals are exposed to them in combination. Most, if not all, essential trace and bulk elements are subject to these types of interactions which can mitigate or aggravate deficiencies or excesses. Mercury, for example, combines with selenium in the soil to form mercury selenide which is very insoluble and, therefore, reduces selenium uptake by crops. As a result, people living in areas with high soil mercury levels tend to suffer unusually high rates of cancer because they are largely denied the beneficial protective effects of selenium.<sup>10</sup> While calcium may, in itself, be protective against many cancers, especially of the digestive tract,<sup>11</sup> it also increases soil alkalinity, encouraging the movement of selenium into crops and animal feed. This, of course, means that people who live in calcareous regions are less likely to be selenium deficient. While road salt may be carcinogenic, it also mobilizes mercury, the selenium antagonist.<sup>12</sup> It is clear, therefore, that in cancer, various substances react together to increase or decrease risk.

Clearly, the impact of environmental variables on health must be studied in combination. What follows is an effort to identify those environmental factors that either individually, or in combinations, trigger development of Alzheimer's disease, especially in those people who are genetically susceptible. Attention is also paid to substances that may be able to block this process.

## ALUMINUM

The best available review of the possible role of aluminum as a trigger for Alzheimer's disease is published by Erik Jansson,<sup>13</sup> in the *Journal of Alzheimer's disease*, in 2001. There is no doubt that aluminum accumulates in the body. It has been estimated, for example, that it is deposited at a rate of some 6 mcg per year in the human brain.<sup>14</sup> As a consequence, autopsies have shown that the brains of normal elderly people, aged between 75 to 101, contain far more aluminum than those of younger people, who died at ages of 32 to 46.<sup>15</sup> Specifically, in this study, each member of the older group had an average of 28 times as much aluminum in their hippocampus and 19 times as much of this metal in their frontal cortex as did those dying younger. Interestingly, although not showing signs of dementia at death, senile plaques and neurofibrillary tangles were common in the elderly and their densities seemed to increase with aluminum levels. Evidence from other autopsies, however, suggest that Alzheimer's disease patients generally tend to have roughly twice the aluminum brain content found in the non-demented of similar ages.<sup>16-17</sup>

Where does all this metal come from? Aluminum forms about 8 percent of the Earth's crust and so is ubiquitous. It has been known to be a human neurotoxin since 1886, when it was discovered to have caused brain damage in Prussian army amputees who had been treated with alum (a double sulphate

of aluminum and potassium) to staunch the bleeding of their wounds.<sup>18</sup> The first animal study to link aluminum to brain damage was published in 1937.<sup>19</sup> There is an extensive literature, reviewed by Jansson,<sup>20</sup> which has established aluminum's role in kidney dialysis, encephalopathy, cognitive impairment, childhood learning disabilities, and brain damage to workers in the welding, coal mining, and smelting industries. All this evidence establishes beyond doubt that aluminum can cause serious brain malfunctions.

Most of the research trying to establish where the aluminum deposits in the aging human brain come from has focussed on dissolved aluminum in drinking water. According to Jansson,<sup>21</sup> by the year 2000, there had been 18 drinking water studies that had linked aluminum levels to elevated Alzheimer's disease and to cognitive impairment of the elderly. In contrast, five epidemiological studies could identify no effect. Jansson,<sup>22</sup> however, points out that most studies claiming no relationship between drinking water levels of aluminum and Alzheimer's disease incidence, prevalence, or mortality involve very low levels of exposure, small sample size, and a lack of inclusion of modifying factors, "making a statistical resolution over background variability unlikely." Simply put, the great bulk of the evidence from epidemiology and geography supports a link between high levels of aluminum in drinking water and elevated incidence of Alzheimer's disease. Those studies that don't are either very small in scale or poorly designed.

Drinking water usually contains between 0.01 and 0.15 mg per litre of aluminum, but some potable water may have as much as 0.40 mg per litre or more.<sup>23</sup> While this represents only a small percentage of total dietary aluminum, it is possible that because of repetitious exposure and increased species solubility, aluminum from drinking water may provide a large component of the total aluminum absorbed. Priest<sup>24</sup> has shown



that the fraction of dietary aluminum entering the tissues may vary from as much as 0.01 for aluminum citrate to 0.0001 for insoluble species, such as aluminum silicates and oxides. Most of this absorbed aluminum tends to be excreted if kidney action is normal, but about 5 percent is deposited in the body, mainly in the skeleton.<sup>25</sup> It was established by Sohler and co-workers<sup>26</sup> as early as 1981, however, that in 400 psychiatric outpatients in New Jersey, memory loss increased as blood aluminum levels rose.

Four geographical studies that clearly support a role for aluminum in Alzheimer's disease will now be discussed in more detail. Martyn and colleagues<sup>27</sup> conducted a survey of 88 English and Welsh county districts to find out the rates of Alzheimer's disease in people under the age of 70. These were estimated from the records of computerized tomographic scanning units. It was found that the risk of developing Alzheimer's disease appeared to be 1.5 times higher in districts where the mean water aluminum concentration exceeded 0.11 mg per litre. There were no such associations between aluminum and other forms of dementia.

Vogt<sup>28</sup> studied links between aluminum in Norwegian drinking water and mortality from both senile and presenile dementia. He estimated that some 50 to 70 percent of these deaths were, in fact, due to Alzheimer's disease and related conditions. Vogt<sup>29</sup> divided Norway into five zones on the basis of the levels of aluminum in lakes, the main source of potable water, and was able to show that as the aluminum content of drinking water rose so too did the death rate from age-related dementia. This cause of death was particularly common in the zone that experienced both elevated aluminum and the highest levels of acid rain. The latter, of course, would raise the solubility of aluminum and increase levels in drinking water. A national survey of the Norwegian Institute of Gerontology also demonstrated

that, within psychiatric nursing homes, counties receiving the worst acid rain accounted for the largest number of dementia patients per 100,000 inhabitants.<sup>30</sup> Four years later, Flaten<sup>31</sup> used more sophisticated techniques, such as correlation and regression analysis, to confirm that in Norway, mortality involving dementia seemed linked to the aluminum content of drinking water.

Clear evidence was provided in 1988 that excess aluminum in potable water can affect memory. An accident at an English water supply plant resulted in drinking water that contained enormously elevated levels of aluminum sulphate being drunk by the local population. Memory loss was an extremely common complaint amongst those unfortunate enough to use such contaminated water.<sup>32</sup> Significant evidence of the link between dementia and aluminum comes from McLachlan's Ontario study involving 668 autopsy-verified Alzheimer's brains.<sup>33</sup> These demonstrated that the risk of developing Alzheimer's disease had been about 2.5 times greater in individuals from communities that drank water that contained more than 100 mcg per litre of aluminum than it had been in those from areas where the potable water had contained less than this level of aluminum.

McLachlan's results were even more spectacular for those who had drunk water that contained 175 mcg per litre of aluminum. Depending on how those patients were grouped, the odds ratio of developing Alzheimer's disease varied from 6.7 to 8.14. That is, their brains were some 7 to 8 times more likely to show the characteristic signs of Alzheimer's disease if such patients had normally consumed water that was very high in aluminum.

Several authors have attempted to quantify the strength of the association between Alzheimer's disease and aluminum. Forbes and McLachlan,<sup>34</sup> for example, studied this link in the very elderly, those aged 85 years or more. They discovered that,

after controlling for six other factors, such as fluoride, silicic acid, iron, pH, and turbidity, those living in districts that supplied drinking water that contained more than 250 mcg of aluminum per litre were almost 10 times more likely to develop Alzheimer's disease. This confirmed an earlier Ontario longitudinal study<sup>35</sup> which established that men 75 years and older, who were drinking water containing at least 0.0847 mg per litre of aluminum, were 1.72 times as likely to show impaired mental functioning. Similarly, after statistical control for five other variables, Alzheimer's mortality displays an odds ratio of 3.54 for those who had drunk water that contained at least 0.336 mg per litre of aluminum.<sup>36</sup> A more recent 8 year longitudinal study involved 3,777 people aged 65 years and older who lived in southwest France in 1988 to 1989. This confirmed that double the risk of developing Alzheimer's disease occurred in those who drank water with an aluminum concentration greater than 0.1 mg per litre.<sup>37</sup>

Looking for a link between Alzheimer's disease and total drinking water aluminum may be too simplistic. In 2000, Gauthier and coworkers<sup>38</sup> described a case control study in which the chemical characteristics of the water historically drunk by 58 elderly Alzheimer's patients were compared with those of potable water used by age and gender matched non-demented controls. This was conducted in the Saguenay-Lac-Saint-Jean region of Quebec. Aluminum specification was assessed using standard analytical protocols. Long-term drinking water exposure (from 1945 to the onset of Alzheimer's disease) was estimated for total, total dissolved Al, monomeric organic Al, monomeric inorganic Al, polymeric Al, Al(3+), AlOH, AlF, AlH(3)SiO(2+)(4), and AlSO(4). While there was no obvious relationship between total aluminum in potable water and Alzheimer's disease, after adjustment for educational level, family cases of the disorder and the APO E4 allele, exposure to monomeric aluminum clearly was associated with this form of dementia (odds ratio 2.67).

The importance of monomeric (single molecule) aluminum has been confirmed again by a more recent study conducted by Prolo and colleagues,<sup>39</sup> in northwest Italy, where the drinking water contained between 5 and 1,220 mcg per litre of total aluminum. Levels of monomeric aluminum, (the type of this element most easily able to enter human cells), ranged from 5 to 300 mcg per litre. These researchers from the University of California at Los Angeles established that Alzheimer's disease was most common where drinking water levels of monomeric aluminum were highest. They also discovered that monomeric aluminum interfered with cell function in cultures, accelerating cell death especially in the presence of beta-amyloid protein.

Not all geographical and epidemiological studies have focused on the role of drinking water aluminum in the etiology of Alzheimer's disease. Aluminum is always present in ambient air, but many industrial workers inhale far more than the 4.4 mcg average daily intake from this source.<sup>40</sup> Such inhaled aluminum appears to be neurotoxic under certain special conditions. To illustrate, silica has a well known ability to protect against aluminum and vice versa. For this reason, between 1944 and 1979, many miners were given aluminum powder as a prophylaxis against silicotic lung disease. An aluminum "bomb" was let off after each shift and the miners inhaled its dust in an effort to protect themselves against silica. During a study conducted during 1988 and 1989, miners who had been exposed to aluminum dust in this way were found to show abnormal cognitive deficits, their neurological problems increasing with the duration of their exposure.<sup>41</sup>

The use of water that contained high levels of aluminum in the treatment of kidney patients was also linked to significant increases in dialysis encephalopathy, a degenerative disorder of the brain that had some similarities to Alzheimer's disease. Parkinson and colleagues<sup>42</sup> demonstrated that in Newcastle,

for example, of the 10 patients in their twenties on home dialysis, none survived for 2 years; all died of dialysis encephalopathy, osteomalacia, or unexplained cardiorespiratory failure.

Beyond this, Rogers and Simon<sup>43</sup> identified an 8.6 fold increased risk of developing Alzheimer's disease amongst residents of the Loretto Geriatric Center of Syracuse, New York who had eaten foods with aluminum additives or that had been cooked or stored in aluminum containers. It is probable, however, that much of the aluminum reaching the brain is absorbed through the skin. Certainly, aluminum applied to the skin of laboratory animals can reach the brain,<sup>44</sup> as can that injected into the nose.<sup>45</sup> It must also be remembered that a wide range of drugs, including antacids and buffered aspirin, and vaccines and deodorants contain aluminum. Most cans are now also made of aluminum and their contents are increasingly polluted with this metal.<sup>46</sup> Nevertheless, Templer, Chicora, and Russell<sup>47</sup> have shown recently that there is a statistically significant association between the US Alzheimer's disease age-adjusted death rate for the period 1979 to 1991, and surficial sediment aluminum concentration, established at the state level by the US Geological Survey. That is, the higher the aluminum levels in soils and sediments, the more elevated the states' Alzheimer's disease death rate. In all races, in people aged 65 and over, the calculated product-moment correlation coefficient was 0.27 ( $p=0.033$ ). This statistical measure was 0.23 ( $p=0.064$ ) in the white population alone.

## SILICA

There is evidence that amorphous aluminosilicates may promote the formation of beta amyloid protein and the senile plaques that are so characteristic of Alzheimer's disease.<sup>48</sup> If this is the case, one might expect that environmental silica

would also promote this form of dementia. Geographical and epidemiologic evidence, however, seems to suggest the reverse. In 1995, Taylor and coworkers<sup>49</sup> published a paper that examined the relationship between silicon and aluminum in the water supplies of northern England and Early Onset Alzheimer's disease. They concluded that as "soluble" silicon rose in such potable water, "soluble" aluminum fell, so that at about 3.5 mg per litre of silicon, aluminum levels were less than 25 mcg in all districts. In addition, those below 65 years of age who drank water that contained more than 3 mg per litre of water-soluble silicon had an odds ratio for developing Early Onset Alzheimer's disease of 0.8, suggestive of a reduction of risk by silicon of 20 percent. The sample size, however, was too small to be considered statistically significant.<sup>50</sup>

Two studies involving silicon and Alzheimer's disease also have been conducted in France. Jacqmin-Gadda and colleagues,<sup>51</sup> for example, examined the relationships between silica and aluminum and early cognitive impairment in 3,777 French elderly, aged 65 years or more. They concluded that:

*The association between cognitive impairment and aluminum depended on the pH and the concentration of silica: high levels of aluminum appeared to have a deleterious effect when the silica concentration was low, but there was a protective effect when the pH and the silica levels were high. The threshold for an aluminum effect, however, was very low (3.5 mcg per litre) and did not support the hypothesis of a deleterious effect for only high levels of aluminum.*

As mentioned previously, Rondeau and coworkers<sup>52</sup> have conducted an 8 year longitudinal follow-up study on the impact of drinking water quality on the mental health of the elderly in southwestern France. Their data showed that silica in excess of 11.25 mg per litre in potable water was associated with

about a 27 percent decline in the risk of developing Alzheimer's disease. All three available studies, therefore, suggest that silica is protective against this form of dementia. Interestingly, aquaculturalists have long been aware that the acute toxicity of aluminum to fish is prevented by silicic acid.<sup>53</sup> This acid is naturally present at high levels in certain waters as a result of the weathering of the aluminosilicates of rocks and minerals and has a strong and unique affinity for aluminum.<sup>54</sup>

## **FLUORIDE**

There is growing evidence that suggests that fluoride is, to some degree, protective against Alzheimer's disease. Still and Kelley,<sup>55</sup> for example, reviewed first admissions of dementia patients, over the age of 55, in three South Carolina hospitals during the period July 1971 to June 1979. Horry County was studied because its water had the highest fluoride content (4.2 mg/litre) of any in the state. In contrast, the water of the other two counties, Anderson and York, had the state's lowest fluoride contents, 0.5 and 0.6 mg/litre, respectively. Only patients with 10 or more years of continuous residence in one of these three counties, prior to hospital admission, were included in the survey. Still and Kelley<sup>56</sup> established that although the annual hospital admission rates for vascular dementia were similar for all three counties, that for Alzheimer's disease in Horry, the high fluoride county, was only one-fifth the average rate of the other two low fluoride counties. This difference was significant at the 0.01 level.

Similarly, in 1986, Liss and Thornton<sup>57</sup> reported on a double-blind randomized trial in which a group of Alzheimer's patients received either a placebo or 40-60 mg of sodium fluoride daily. Twelve patients who had been study participants were 'decoded' after 30 to 36 months. In 11 of 12 cases the researchers were

correctly able to identify whether the patient had received fluoride or the placebo. This was possible because, it was claimed, there had been an observable difference in the rate of progression of the symptoms between the two groups, with those receiving fluoride deteriorating more slowly.

In 1991, Forbes and coworkers<sup>58</sup> interviewed surviving members of the Ontario Longitudinal study of Aging and identified 285 who displayed evidence of mental impairment. A further 280 individuals were selected from the same cohort who were matched for both age and gender but showed no sign of mental impairment. Water quality information was then collected about the places of residence of all participants in the study. Forbes and colleagues<sup>59</sup> identified high and low aluminum and fluoride drinking water, divided according to concentrations below or above the 50<sup>th</sup> percentile. It was found, for example, that in men the relative risk of mental impairment varied with the aluminum and fluoride content of the drinking water traditionally drunk by the study participant. Mental impairment was greatest in high aluminum-low fluoride areas (odds ratio 2.7) and lowest in high fluoride areas (odds ratio 0.7). Indeed, the level of fluoride in drinking water seemed more important than the level of aluminum as an indication of the risk of developing mental impairment. In a later paper about the same study, Forbes and coworkers<sup>60</sup> provided new data for 'impaired mental functioning.' These had been derived from a logistic regression model, in which the odds ratios for high aluminum and high fluoride were 1.86 and 0.58 respectively. That is, aluminum appeared to promote, and fluoride protect against, Alzheimer's disease.

Two later studies in which Forbes<sup>61-62</sup> was involved also both confirmed that the probability of developing Alzheimer's disease decreased as drinking water fluoride levels rose. The first of these was a longitudinal study of 75-year-old Canadians



and provided data that indicated that fluoride equal to, or in excess of, 0.88 milligrams per litre was associated with a 36 percent reduction in the risk of developing Alzheimer's disease. Results of a second research project published by Forbes and McLachlan,<sup>64</sup> of 85-year-old Canadians, indicated that drinking water that contained fluoride levels of 0.5 to 0.98 mg per litre reduced Alzheimer's risk by some 30 percent.

## **CALCIUM AND MAGNESIUM**

Calcium plays a pivotal role in cells, especially neurons, since it is involved in the release of neurotransmitters, neuronal cytoarchitecture, nervous system growth and development, and intra cellular communication and signal processing.<sup>65</sup> There is a growing literature that suggests a significant role for calcium abnormalities in Alzheimer's disease. These articles and books include at least two volumes on the topic published by the New York Academy, namely *Calcium Hypothesis of Aging and Dementia and Calcium, Membranes, Aging, and Alzheimer's disease*.<sup>67</sup>

As a result of calcium's strong affinity for fluoride, most of the latter element in the Earth's crust is found as a constituent of one of two calcium compounds, fluorite ( $\text{CaF}_2$ ) and fluorapatite ( $\text{Ca}_{10}(\text{PO}_4)_6\text{F}_2$ ). The antagonism between calcium and fluoride also influences human health. It has been shown in China, for example, that the prevalence of endemic fluorosis is not simply a reflection of the level of fluoride in drinking water. Prevalence is also affected by other factors, including the amount of calcium and vitamins C and D in food and the calcium content of potable water.<sup>68</sup> Of course, this antagonism between fluoride and calcium is demonstrated further by the use of bone char as an absorbent medium in defluoridation plants. A comparable process also seems to occur in the human body where fluoride is removed rapidly from serum and deposited in bones

and teeth. As a consequence, under steady-state conditions, 99 percent of the fluoride in the body is sequestered in calcified tissues. Most of the rest occurs in the plasma and is available for excretion.<sup>69</sup>

Given this obvious antagonism between fluoride and calcium one might expect that because the former seems to be protective against Alzheimer's disease, the latter element would promote it. However, the available evidence seems to suggest otherwise. Yase and coworkers<sup>70</sup> have studied the high incidence of amyotrophic lateral sclerosis (which can be associated with Parkinsonian features and dementia), in the Kii Peninsula of Japan, since the early 1960s. The brains of such patients can display neurofibrillary tangles identical to those seen in Alzheimer's disease, both in the cerebral cortex and in the brain-stem nuclei.<sup>71</sup> Interestingly, the water of the two disease foci in the Kii Peninsula is exceptionally low in both calcium and magnesium. This also appears to be true of similar foci of amyotrophic lateral sclerosis and Parkinsonism with dementia found in Guam and Western New Guinea.<sup>73</sup> The waters of the Kii Peninsula are noted for their crystalline transparency and Fujita<sup>74</sup> claims that, because of a lack of mineralization, the Koza River is unable to support fish. Garruto and colleagues<sup>75</sup> have analysed numerous drinking water samples from areas with high incidences of amyotrophic lateral sclerosis in the Kii Peninsula and have found them to be exceptionally deficient in both calcium and magnesium. Potable water from these regions generally contained less than 1 to 2 ppm calcium and below 1 ppm magnesium. The significance of the deficiencies has been recently demonstrated by Kihira and coworkers,<sup>76</sup> who have established that chronic low calcium and magnesium, high aluminum diet induces neuronal loss in mice. This is not really such a new discovery since in 1992, Armstrong and colleagues<sup>77</sup> used such a diet to increase the negative effects of aluminum on mouse brain bipterins.

Further evidence that calcium does not promote and may reduce the risk of developing Alzheimer's disease was provided by Jacqmin and coworkers<sup>78</sup> in their study of 3,777 French men and women, 65 years or older. They discovered a significant protective effect against cognitive impairment in those elderly who drank water containing 75 milligrams per litre or more of calcium.

## **DRINKING WATER pH**

Whatever is triggering Alzheimer's disease appears to be very sensitive to water pH. Three studies, conducted by Forbes and his colleagues in Ontario, established that drinking water with a pH in excess of 7.85 is associated with a reduction in the risk of developing this type of dementia. To illustrate, in 1994, data was published from the Ontario Longitudinal study of Aging that showed that potable water with a pH value of between 7.85 and 8.05 was associated with a 60 percent reduced risk of the development of impaired mental functioning, in 75-year-old men.<sup>79</sup>

This water pH-Alzheimer's disease link was supported further by Forbes<sup>80</sup> later publication based on an analysis of death certificates of former volunteers in this longitudinal study. These documents were used to establish that, in Canada, water pH in the range of 7.85 to 7.95 had been linked to a 30 percent reduction in Alzheimer's disease mortality rates, when compared with consumption of both more acid and alkaline potable waters. The relationship between water pH and this form of dementia appeared to form a U-shaped curve. Further support for the value of drinking water that had a pH in excess of 7.85 was provided by Forbes and McLachlan<sup>81</sup> who showed it to be associated with approximately a 50 percent reduction in Alzheimer's disease risk in the very elderly. Jacqmin-Gadda

and coworkers<sup>82</sup> also established that the impact of high aluminum on elderly cognitive impairment in the French was linked to both the pH and silica content of their drinking water. The odds ratio for elderly mental impairment, for example, was 1.30 in water districts that supplied a product that was high in aluminum but low in both pH and silica. In contrast, those drinking high aluminum water that also was elevated in both pH (above 7.35) and silica had only a 0.75 odds ratio of developing elderly cognitive impairment.

## **SUMMARY**

The great bulk of evidence from numerous geographical and epidemiological studies supports a strong link between aluminum consumption, especially monomeric aluminum from drinking water, and an elevated incidence of Alzheimer's disease. The negative impact of aluminum, however, appears mitigated by silicic acid, calcium, and magnesium, especially in potable water with a pH of between 7.85 and 8.05. Acidic drinking water that is high in aluminum and lacking in silicic acid, calcium, and magnesium seems to be particularly dangerous. Fluoride also may protect against Alzheimer's disease when the pH is high.

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*The value of what one knows is doubled if one confesses to not knowing what one does not know. What one knows is then raised beyond the suspicion to which it is exposed when one claims to know what one does not know.*

Schopenhauer

## CHECKING OUT ALTERNATIVES

*Knowing is not enough; we must apply.  
Willing is not enough; we must do.*

Goethe

In his book *The 100: A Ranking of the Most Influential Persons in History*, Michael Hart<sup>1</sup> argues that Thomas Edison should occupy 38<sup>th</sup> place. That puts him one rank below the economic theorist Adam Smith and one above Antony van Leeuwenhoek, discoverer of microbes. Edison had more than 1,000 patents. He invented, among other things, the stock ticker, the phonograph, a practical incandescent light bulb, and its associated electric power distribution network. How could one inventor be so creative? Edison progressed by trial and error, always searching for something that worked. That is, he believed more in what later came to be known as Lateral Thinking<sup>2</sup> than he did in the Scientific Method. Alternative medicine has evolved in a similar manner. For millennia, illnesses have been treated with a wide diversity of herbs, stone drugs, animal parts, exercises, magnetic fields, and other techniques. Eventually, those approaches that worked well are retained. Those that fail to benefit the patient are abandoned. At any one time, alternative medicine, therefore, includes numerous potential approaches to specific disorders or diseases. Some may be extremely effective, others useless or even very harmful. What is described in this chapter are current alternative treatments for Alzheimer's disease that may, or may not, be beneficial. Supporting evidence for their use is provided where this is available.

## HERBS

### Sage

Sage (*Salvia lavandulaefolia*) has been promoted by herbalists, such as John Gerard and Nicholas Culpeper, as a memory stimulant for hundreds of years. It is currently added to foods and used to produce herbal teas. Scientific research is beginning to support its benefits for those suffering memory loss, probably because it inhibits the enzyme acetylcholinesterase, which breaks down the neurotransmitter acetylcholine.<sup>3</sup> It may be recalled that a shortage of acetylcholine is characteristic of Alzheimer's patients.

### **Bacopa monniera (Bacopa)**

Bacopa is an Ayurvedic herb which is claimed to have anti-fatigue, anti-anxiety, and memory-strengthening properties.<sup>4</sup> It is also used in the treatment of epilepsy. In a study of its effects on a culture of purified rat astrocytes, bacopa has been shown capable of protecting against nitric oxide induced oxidative stress and DNA damage in a dose dependant manner.<sup>5</sup> The researchers involved concluded that their results were consistent with the use of this medicinal plant in the treatment or prevention of neurological illnesses, including Alzheimer's disease.<sup>6</sup> Bacopa also has been shown to have significant anti-depressant effects in rats.

### **Ginkgo biloba**

Ginkgo biloba is used in alternative medicine for a variety of reasons, including prevention of altitude sickness, improvement of blood circulation, and enhancement of memory. While nearly every arboretum or botanical gardens has a Ginkgo tree, supreme specimens are usually restricted to temple grounds

in Japan, China, and Korea. Some of these ancient trees are thought to be over 2,000 years old and have been venerated for their medicinal properties for millennia.<sup>8</sup> Animal studies using transgenic mice recently have confirmed the positive impact of *Ginkgo biloba* on memory,<sup>9</sup> perhaps due to its ability to reduce the oxidative damage caused by free radicals.<sup>10</sup> As a result, medical trials have been conducted to investigate whether, or not, ginkgo is useful in the treatment of Alzheimer's disease. These too have generally proven positive, as for example, a large multi-centre clinical German trial conducted by Kanowski and Hoerr.<sup>11</sup> This growing body of evidence of the value of *Ginkgo* in memory loss has encouraged its use in the treatment of early-stage Alzheimer's disease by conventional physicians.<sup>12</sup>

### **Vinpocetine**

Vinpocetine is a synthetic ethyl ester of apovincamine, an alkaloid obtained from the leaves of the Lesser Periwinkle (*Vinca minor*).<sup>13</sup> It is thought to be an excellent vasodilator and cerebral metabolic enhancer. Data from cells treated with beta amyloid suggests that it can protect against amyloid beta-peptide toxicity and prevent excessive oxidative stress.<sup>14</sup> Despite these promising characteristics, 15 Alzheimer's patients treated with increasing doses of vinpocetine, ranging from 30 to 60 mg per day, for one year, developed cognitive deficits that were similar to an untreated control group.<sup>15</sup> As a consequence, Thal and coworkers<sup>16</sup> concluded that "vinpocetine is ineffective in improving cognitive deficits and does not slow the rate of decline in individuals with Alzheimer's disease."

### **Huperzia serrata**

Huperzine A is an alkaloid isolated from the Chinese moss *Huperzia serrata*. It has been found to cross the blood-brain barrier easily and act as a potent, yet reversible cholinesterase

inhibitor.<sup>17</sup> As a result, it, like sage, appears able to increase acetylcholine availability. *Huperzia serrata* has been collected in the colder regions of China for centuries and used to treat fever and inflammation.<sup>18</sup> Animal studies have shown that an extract from it, Huperzine A, can help protect against both brain injury and memory loss.<sup>19</sup> Beyond this, a double-blind study of 50 Alzheimer's patients receiving either a placebo or 0.4 mg of Huperzine A daily, for 8 weeks, showed statistically significant memory, cognitive, and behavioural improvements in those receiving the extract.<sup>20</sup> The researchers suggested that Huperzine A was a promising, safe new treatment for Alzheimer's disease. It is noted in the literature that high doses might prove more toxic. Huperzine A has been approved as the drug of choice for the treatment of Alzheimer's disease in China, while in North America it is still marketed as a dietary supplement.<sup>21</sup>

## **Galantamine**

Galantamine is a natural supplement derived from the snowdrop.<sup>22</sup> The common snowdrop from which this substance is produced is closely related to the daffodil, which also has been shown to be an effective inhibitor of acetylcholinesterase. In a double-blind, placebo controlled trial conducted in both Europe and Canada, 653 patients with mild to moderate Alzheimer's disease were provided with either Galantamine or a placebo. After 6 months, it was clear that the snowdrop extract was slowing declines in cognition and functional ability, with little sign of adverse effects.<sup>23</sup> Similarly, in a second study involving patients diagnosed with Alzheimer's disease and cerebral vascular disease, 285 were given either 24 mg per day of Galantamine or a placebo. After 1 year, those receiving the Galantamine had showed clinically significant improvements in cognitive functions which they maintained throughout the year. In the placebo group, cognitive functions had deteriorated.<sup>24</sup> The results of a series of other trials<sup>25-27</sup> have been published recently.

All appear favourable and Galantamine is now approved for the treatment of Alzheimer's disease in Canada<sup>28</sup>.

### **Lion's Mane mushroom (*Hericium erinaceum*)**

The Canadian fungus Lion's Mane mushroom contains at least two compounds, hericenones and erinacines, that strongly stimulate Nerve Growth Factor (NGF) *in vitro*.<sup>29</sup> Both of these compounds probably can cross the blood-brain barrier and may be able to encourage Nerve Growth Factor production in the brain. Nerve Growth Factor is a member of a group of proteins that plays a key role in the maintenance, survival, and regeneration of neurons during adult life. Animal studies have shown that mice lacking Nerve Growth Factor develop a condition resembling Alzheimer's disease.<sup>30</sup> In an effort to discover whether hericenones and erinacines were of value to Alzheimer's patients and others with neurological diseases and disorders, 50 Japanese patients were given 5 grams of dried Lion's Mane mushroom daily in soup for a 6 month period.<sup>31</sup> A further 50 patients acted as controls. The results of this preliminary study that included seven dementia patients were promising. All seven showed improvements in physical capabilities. Six improved also in understanding, communication, and memory skills. Preliminary findings suggest that Lion's Mane mushroom is a potent inducer of brain tissue regeneration that may be of considerable value in the treatment of Alzheimer's disease.

## **MINERALS**

### **Calcium and Magnesium Ascorbate**

Research suggesting a notable breakthrough in the prevention of Alzheimer's disease was described by Dr. Natalia Bobkova,<sup>32</sup> in June 2001, at the III World Congress on Vitamin C. Bobkova



is a member of the Russian Academy of Sciences research group that had been screening the elderly for signs of early memory loss. Those older Russians found to be experiencing the greatest declines were given the B vitamins, together with elevated levels of several mineral ascorbates, specifically potassium, magnesium, calcium, zinc, manganese, and chromium ascorbates. These, of course, provided such elderly patients with high levels of vitamin C and very easily absorbed minerals. According to Bobkova, in every case memory returned to normal in a few weeks.

Galeev and coworkers<sup>33</sup> described a similar study in which 52 to 78 year old patients who had complained of failing memory and deteriorating cognitive functions were provided with 1 to 2 grams of Alacer Corp's Emer'gen-C and Super Gram II mineral ascorbates. Fifteen such patients were tested after receiving these supplements for 1 month and 13 after 2, 3, 5, 7, 9, 12, and 18 months. Initially, a control group was used to compare the effects of such mineral ascorbate supplementation. However, after psychophysiological testing showed marked improvements in those receiving Emer'gen-C and Super Gram II but not in controls, the latter group also were provided with these minerals and subsequently began to display significant memory and cognitive function benefits.

Bobkova and colleagues<sup>34</sup> also described a related animal experiment in which mineral ascorbates were given to mice after olfactory bulbectomies had been carried out. Olfactory bulbectomy involves an operation to destroy an animal's ability to smell. In untreated animals, subjected to this operation, a deficit in memory occurs, accompanied by various neurodegenerative processes in brain structures that appear to mimic those of Alzheimer's disease. Bobkova and coworkers, however, found the mineral ascorbates prevented this memory loss, and protected the neurons of the temporal cortex from degenerative

changes. These observations may explain why mineral ascorbates can reverse early memory loss in the elderly, as described at the III World Congress on Vitamin C, in 2001.<sup>35</sup>

## **Lithium**

Low dose lithium is used as an alternative treatment for the early stage of Alzheimer's disease.<sup>36</sup> There are several good reasons this mineral may be beneficial. Lithium is known to slow the formation of beta amyloid<sup>37-38</sup> and reduce the damage caused by this protein, even after it has been secreted.<sup>39</sup> Beyond this, it also inhibits the formation of tau and neurofibrillary tangles.<sup>40</sup> This may be because lithium is an effective electrolyte for aluminum detachment and helps to chelate this metal so it can be more readily removed from the body. Lithium also inhibits the formation of abnormal "crosslinks" caused by aluminum.<sup>41</sup>

## **AMINO ACIDS**

### **Acetyl-l-carnitine**

Acetyl-l-carnitine is derived from carnitine, which consists of two amino acids, lysine and methionine. It is known to be active at cholinergic neurons, help with membrane stabilization, and improve mitochondrial function.<sup>42</sup> Although some studies suggest it slows the progression of Alzheimer's disease, evidence from others disputes this. Pettegrew and associates,<sup>43</sup> for example, gave 3 grams of acetyl-l-carnitine to seven Alzheimer's patients daily for a year. Five similar controls were given a placebo. While all 12 probable Alzheimer's patients had virtually identical cognitive scores at the beginning of the year, by the end of it, the group of patients receiving acetyl-l-carnitine had significantly higher test performances. This was because the control group had deteriorated, while the acetyl-l-carnitine

group maintained their earlier cognitive abilities. In contrast, a double-blind, placebo-controlled trial involving 229 probable Alzheimer's patients found no significant differences, after 1 year, between those receiving acetyl-L-carnitine and those who did not.<sup>44</sup> A recent *Cochrane Database of Systematic Reviews*, by Hudson and Tabat,<sup>45</sup> concluded that acetyl-L-carnitine is unlikely to be an important therapeutic agent in Alzheimer's disease but still called for more research into the subject.

## LIPIDS

### Phosphatidylserine

Another memory aid, phosphatidylserine is a lipid – a fat, or fat-like, molecule found in all functioning cells but concentrated in the brain. Recent clinical research appears to support its use by those experiencing cognitive difficulties. To illustrate, in 1991, in a study coordinated by the Memory Assessment Clinic of Bethesda, Maryland,<sup>46</sup> 149 elderly volunteers were given either phosphatidylserine or a placebo for 12 weeks. Those receiving the nutrient showed significant improvements in both memory and the ability to perform tests. In a follow-up study, Crook and coworkers<sup>47</sup> provided 51 Alzheimer's patients with either phosphatidylserine or a placebo for 3 months. Those receiving the lipid improved on several cognitive measures, suggesting that phosphatidylserine may be a useful treatment in the early stages of Alzheimer's disease. Cenacchi and colleagues<sup>48</sup> took this research further by providing 300 mg of phosphatidylserine daily, or a placebo, to 494 elderly geriatric patients who were suffering from cognitive impairment. These were drawn from 23 health care facilities located in northeastern Italy. The study continued for 6 months, by the end of which time those patients being given phosphatidylserine showed statistically significant improvements in both memory

and behaviour. The reason for this occurrence seems to have been established by Heiss and colleagues,<sup>49</sup> who used positron emission tomography (PET) to show that phosphatidylserine stimulates the cerebral metabolic rate for glucose. It may be recalled that a deficiency in glucose metabolism is characteristic of those suffering from Alzheimer's disease.

## **SUMMARY**

It seems likely that several of the herbs traditionally used to treat memory loss have some benefits for Alzheimer's disease patients. Sage, for example, inhibits the enzyme acetylcholinesterase, which breaks down acetylcholine. Bacopa reduces nitric oxide induced oxidative stress and mitigates depression. Ginkgo biloba also appears able to reduce free radical damage, as may vinpocetine. The Chinese medical establishment feels that Huperzine A, a moss extract, has shown enough promise in the treatment of Alzheimer's disease to recommend it to physicians for this purpose.

The research being carried out jointly by members of the Russian Academy of Sciences and the Committee for World Health, using high dose ascorbate minerals, is also very impressive. Ascorbate minerals appear capable of reversing early-stage memory loss, while lithium may be able to inhibit the formation of senile plaques and neurofibrillary tangles. The B vitamins, especially folic acid, niacin,<sup>50</sup> and B<sub>12</sub> also may be of use in protecting against memory loss.

The value of acetyl-l-carnitine in the treatment of Alzheimer's disease is less obvious, since clinical trials have been contradictory. In contrast, phosphatidylserine appears to have the potential to stimulate glucose metabolism, known to be deficient in Alzheimer's patients.

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*Ideology, like theater, is dependent on the willing suspension of disbelief. At the core of every ideology lies the worship of a bright new future, with only failure in the immediate past. But once the suspension goes, willingness converts into suspicion – the suspicion of the betrayed. Our brilliant leaders abruptly appear naive, even ridiculous.*

J.R. Saulo, *The Collapse of Globalism*, 2004  
*Harper's Magazine*

*We're pushing our bodies past their own innate limits. Due to extraordinary medical interventions in cancer, heart disease, and other conditions, humankind is now living longer than our genes would ordinarily allow. We are outliving our own mortality signature, living on what epidemiologists call "manufactured time." It is the cushion of extra life that we are creating for ourselves with our ingenuity and our tools. The real challenge, of course, is to ensure that this new time is something we are happy to have.*

D. Shenk<sup>1</sup>

### THE FAMILY PHYSICIAN

A recent study conducted by Donna Cohen,<sup>2</sup> a professor at the University of South Florida, showed that of the 1,500 to 2,500 murder/suicides that occur each year in the USA, 21 percent involve the elderly. In the most typical case, a depressed husband who is caring for a wife with Alzheimer's disease, or some other debilitating condition, kills her and then shoots himself. Cohen<sup>3</sup> is quoted as saying:

*What may at first appear as an act of love and mercy is more likely an act of depression and desperation .... These acts are not impulsive. Normally, the man has been planning the event for a long time, and most of these tragedies occur in homes rather than in hospitals or nursing homes.*

The truth is, being a care provider for a progressively declining Alzheimer's patient is a thankless, mentally and physically draining task which conventional medicine currently only can make worse. This is because it offers no effective treatment, merely drugs which, to the detriment of both caregivers and society, prolong this process of mental and physical decline. Indeed, most people, myself included, if asked (when in full possession of their mental faculties) whether they wanted such an extended death would almost certainly opt for a more rapid demise. In short, the current medical treatment of Alzheimer's disease benefits no one, or nothing, except the medical profession and the pharmaceutical industry. Until we prevent or halt and effectively reverse Alzheimer's disease, this will continue to be the case.

## **PROLONGING THE PROGRESSION**

A variety of medications are used currently to delay symptom progression in Alzheimer's disease. The most widely accepted are donepezil (Aricept) and tacrine (Cognex).<sup>4</sup> Both drugs are cholinesterase inhibitors, that is they interfere with the cholinesterase enzyme, acetylcholinesterase, which breaks down the neurotransmitter acetylcholine. Nerve fibres, that is neurons, are stimulated or inhibited by the endless firing of signals across synapses (rated like electric switching centres). Such stimulating signals are often carried by acetylcholine and discontinued by the enzyme acetylcholinesterase, which breaks down acetylcholine.<sup>5</sup> The Alzheimer's drugs donepezil and tacrine, therefore, seek to reduce the activity of the inhibitor acetylcholinesterase in order to increase the neurotransmitter acetylcholine. This is logical. As may be recalled, in Alzheimer's disease, certain neurons, found at the base of the brain, known as the Nucleus Basalis of Meynert, die. Since such neurons produce acetylcholine, there is, as should be

expected, a deficiency of this neurotransmitter in the brains of Alzheimer's patients. Clearly, you would expect such patients to benefit if acetylcholine levels rose. However, previous chapters of this book also have shown that, in dementia, biological abnormalities are not limited simply to acetylcholine, but also include numerous other neurotransmitters, for example, glutamate, dopamine, norepinephrine, and serotonin. Several other hormones and mineral levels in the Alzheimer's disease brain are also atypical. It is not surprising, therefore, that drugs, such as donepezil and tacrine, that aim to impose acetylcholine balance are only of marginal value, since many other biochemical abnormalities remain unaddressed. As a consequence, effects are modest and results are considered successful if either drug returns the patient's ability to function to the level possessed 6 to 12 months earlier. The use of tacrine, for example, has been shown to delay the need for nursing home admittance.<sup>6</sup>

Other cholinesterase inhibitors that are also designed to enhance neuronal transmission by increasing acetylcholine at receptors include Galantamine, rivastigmine, and metrifonate.<sup>7</sup> However, since all such drugs address only one abnormal aspect of Alzheimer's disease biochemistry, it is not surprising that their benefits tend to be relatively limited.<sup>8</sup>

Memantine, a low- to moderate-affinity, noncompetitive N-methyl-D-aspartate receptor antagonist has been used in German clinics for over 10 years to treat patients with dementia.<sup>9</sup> This drug often is used in combination with acetylcholinesterase inhibitors such as donepezil.<sup>10</sup> The major value of memantine is that it is designed to protect against the excitotoxicity of low glutamate concentrations. As would be expected, addressing biochemical imbalances in the cholinergic and glutamatergic systems simultaneously appears to have some added value in the treatment of Alzheimer's disease.<sup>11</sup>

In addition to cholinesterase inhibitors and memantine, several nonspecific drugs also are being used to try to delay progression in Alzheimer's disease. To illustrate, at least three longitudinal studies have suggested that estrogen replacement therapy may have a protective effect against dementia and, as a result, it is being used by physicians to treat Alzheimer's disease.<sup>12</sup> Some research supports the use of this medication. Lambert and colleagues,<sup>13</sup> for example, have studied in vitro binding between estrogen receptors and fragments of the human APO E gene. It may be recalled this gene appears involved in determining much of the genetic risk of developing Alzheimer's disease. Their results suggested that the significance of the APO E4 allele may be influenced by estrogen. Beyond this, Granholm and coworkers<sup>14</sup> have shown that in the mouse model of Downs syndrome, estrogen alters the amyloid precursor protein. It will be recalled that this protein appears to play the key role in the formation of the senile plaques that are so characteristic of Alzheimer's disease brains.

Nevertheless, the largest clinical trial completed to date, conducted by Mulnard and colleagues<sup>15</sup> from the University of California's Institute for Brain Aging and Dementia, does not support the use of estrogen in the treatment of Alzheimer's disease. Between October 1995 and January 1999, 120 women suffering from mild to moderate Alzheimer's disease were given randomly either estrogen (0.625 mg per day or 1.25 mg per day) or a placebo for one year. Their memory, attention spans, language skills, motor functions and "activities of daily living" were monitored and compared on several subsequent occasions. All these women previously had undergone a hysterectomy. The results caused these researchers to conclude that estrogen did not improve global, cognitive or functional outcomes in women with mild or moderate Alzheimer's disease. With such treatment there was no slowing of disease progression which may, if anything, have been worsened by estrogen therapy.

There may be a case for the use of the hormone testosterone in the treatment of Alzheimer's disease, although as yet it is not widely used. This is because the impact of testosterone on the risk of developing Alzheimer's disease is still unclear. In 2003, Almeida and Flicker<sup>16</sup> published a paper entitled "Testosterone and dementia: Too much ado about too little data" in *The Journal of the British Menopause Society*. In it they pointed out that test tube and animal studies have suggested that testosterone protects neurons and can reduce the levels of beta-amyloid and the phosphorylation of tau. That is, testosterone can reduce neural damage and slow down the formation of both senile plaques and neurofibrillary tangles, all of which are characteristics of Alzheimer's disease. Unfortunately, the results of a small number of cross-sectional studies and five randomized trials of testosterone treatment on healthy older men have been inconsistent and, at best, demonstrated that this hormone has a weak association with memory scores.<sup>17</sup> Beyond this, the serum levels of testosterone in male Alzheimer's patients are very like those of similarly aged men without the disorder, and so are brain levels of the hormone. Almeida and Flicker,<sup>18</sup> therefore, concluded that "...currently available evidence does not support the existence of a strong association between testosterone and cognitive function/AD [Alzheimer's disease]."

Two more recent studies add further confusion to the picture. Hoskin and coworkers<sup>19</sup> measured levels of sex-hormone binding globulin in the serum of 576 women aged over 65. Elevated levels were found in those who were Alzheimer's patients, suggesting that they had higher than normal blood testosterone and estrogen. In contrast, in 574 men followed for about 19 years as part of the Baltimore longitudinal study of aging, elevated free blood testosterone was associated with a reduced risk of developing Alzheimer's disease.<sup>20</sup> The relationship between testosterone and Alzheimer's disease risk is still uncertain and controversial.<sup>21</sup> It also should be pointed out that

there is a possibility that testosterone supplements may promote stroke and prostate cancer.<sup>22</sup>

Nonsteroidal anti-inflammatory drugs (NSAIDs), including aspirin and ibuprofen, also have been linked to a lower incidence of dementia.<sup>23</sup> It is as yet unclear whether this is because they reduce the brain inflammation seen in Alzheimer's disease or protect against stroke. Beyond this, Alenog and colleagues<sup>24</sup> have shown that in mixed rat cell cultures, the common non-steroidal anti-inflammatory drugs aspirin and indomethacin induced significant increases in extracellular apolipoprotein E levels. As will be recalled this is involved in senile plaque formation in Alzheimer's disease.

Etminan, Gill, and Samii<sup>25</sup> recently have conducted a meta-analysis of all the studies that have examined the possible effects of non-steroidal, anti-inflammatory drugs on the risk of Alzheimer's disease. There have been nine in all. Six were cohort studies with a total of 13,211 participants and three case-control studies with 1,443 volunteers involved. The evidence suggests that taking such drugs does reduce the risk of Alzheimer's disease. To illustrate, the risk of developing this type of dementia declines with the time for which they have been taken, the relative risk dropping to a very impressive 0.27 among long term (mostly over 2 years) users. The pooled relative risk in eight studies of subjects taking aspirin was 0.87. Nevertheless, to quote Sloane,<sup>26</sup> "Because of the risks of NSAID use, which include gastrointestinal and renal toxicity, these agents cannot be routinely recommended for use as a preventative measure against Alzheimer's disease at the present time." Gastrointestinal bleeding is one significant risk associated with prolonged use of non-steroid anti-inflammatory drugs.

Selegiline (deprenyl), a monoamine oxidase-B inhibitor that may reduce oxidative stress,<sup>27</sup> also has been used in the treatment

of Alzheimer's patients.<sup>28</sup> Birks and Flicker<sup>29</sup> have recently conducted a meta-analysis of selegiline's impact on Alzheimer's disease as demonstrated by all available clinical trial evidence. They concluded that there is no evidence of a clinically meaningful benefit for Alzheimer's disease sufferers from the use of selegiline. They also suggest that its use as a treatment for this form of dementia be halted.

Vitamin E, the benefits of which have been described previously, is also prescribed by some physicians since it has far fewer adverse effects than selegiline. Dosages of up to 2,000 IU daily are used.<sup>30</sup>

## **SUMMARY**

A variety of drugs are used routinely to treat patients suffering from Alzheimer's disease. The evidence supporting their value is mixed. Some, such as the cholinesterase inhibitors donepezil and tacrine, appear to slow disease progression by a few months. Others, including selegiline, may have little, if any, beneficial effect on this form of dementia. It is interesting that the best case of real value appears to be for non-steroidal anti-inflammatory drugs, such as aspirin and ibuprofen, which physicians hesitate to use to reduce the risk of developing Alzheimer's disease as they can cause serious gastrointestinal and renal toxicity. It can be argued that since the drugs in common use merely prolong disease progression, they are of no real benefit to either patients or caregivers and simply increase the cost of the Alzheimer's disease "pandemic" to society. Obviously, what is needed are new approaches that either completely prevent, or quickly reverse, this form of dementia.



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*All living organisms require a regular supply of nutrients. This is true for microbes as it is for man. If there is a deficiency, or an excess, in fact if there is an imbalance of nutrients, then normal development will cease, and abnormal development will result. If the imbalance is severe death will eventually result.*

K.H. Schutte, *The biology of the trace elements*, 1979

*Abide with me; fast falls the eventide;  
The darkness deepens; Lord with me abide;  
When other helpers fail, and comforts flee,  
Help of the helpless, O, abide with me.*

*Swift to its close ebbs out life's little day;  
Earth's joy grows dim, its glories pass away;  
Change and decay in all around I see;  
O thou who changest not, abide with me.*

Henry F. Lyte (1847)

*Abide With Me*

As Siegel<sup>1</sup> points out, “we should be paying more attention to the exceptional patients, those who get well unexpectedly, instead of staring bleakly at all those who die in the usual pattern.” I first used this quotation from *Love, Medicine and Miracles* in 1988, in a paper entitled “Lifestyle changes and the ‘spontaneous regression’ of cancer: An initial computer analysis.”<sup>2</sup> The idea behind this article was very simple. I used a questionnaire to collect information from 200 published accounts of spontaneous regression that included patients’ treatment(s), dietary and lifestyle changes, mineral, vitamin, and herbal supplements, and detoxification procedures. This approach generated a great deal of useful new information, which was analysed using simple statistics. It served to stimulate numerous hypotheses that may eventually help to account for “spontaneous” cancer regression. I used a similar approach in *What really causes schizophrenia*<sup>3</sup> to collect information from the testimonies of 50 recovered schizophrenics.

Naïvely, I considered using it again to examine what recovered Alzheimer's patients had done that might account for their reversal of this type of dementia. I soon found it to be an impossible approach since so few people ever come back from this particular abyss. Indeed, I could find only two convincing cases of the "spontaneous" regression of Alzheimer's disease. Fortunately, however, both of those concerned had written books about their experiences.<sup>4-5</sup> These cases are now reviewed but in a very short chapter.

The following material is abstracted from the prologue of Louis Blank's<sup>6</sup> autobiographical book, *Alzheimer's Challenged and Conquered?*. It shows how serious his memory loss had become and how deep he must have been into the Early Stage of Alzheimer's disease when the events described took place. They occurred when he was taking an elevator to his apartment.

*The young woman interrupted my thoughts as she said something to me. I pretended to ignore her, but she spoke louder so I looked up so as not to appear impolite... When I was young, a lady would not speak to a strange man until someone introduced him to her...The couple got out at the ninth floor, and I was alone with the young woman. She was now looking at me openly, with a quizzical expression on her face.....Keeping my eyes averted, I fled through the doors as soon as they opened and I sensed, even without seeing her, that she had got out as well. "She might be visiting someone on my floor," I thought. "Strange, most of the people on this floor are still at work." I put my key in the lock and opened the door. Suddenly, I was uncomfortably aware that the strange woman was right behind me. I tried to close the door but she put out her hand and held it open. "W...what do you want?" I stammered. "I want to come in, of course." Her brazen cheek took me aback. "What do you mean, you 'want to come in'?" "I've come to visit you, Dad. What's the matter? You look as if you don't know me."*<sup>7</sup>

Louis Blank could no longer recognize his own daughter. It was later confirmed, after detailed hospital testing,<sup>8</sup> that he had Alzheimer's disease. As his disorder progressed, he completely lost the ability to recognize his own family or to speak, and to dress, wash, or eat without assistance. For 6 months, at the peak of his illness in 1993, he sat virtually motionless. His recovery appeared to begin after his family replaced all its aluminum cooking utensils and started to avoid aluminum cans. In addition, he was fed a high magnesium diet, designed to chelate aluminum. By May of 1994, Louis Blank was once again able to carry on conversations and venture outside, and by January of 1996, he had written and published his book, *Alzheimer's Challenged and Conquered?*,<sup>9</sup> despite the fact that one of his specialists continued to argue that since there is no cure for Alzheimer's disease, he must still have it. An interesting aspect of Blank's description of his experiences is that, while most of his long-term memory remains, he still has no recollections of his worst 6 months. This confirms that, as Alzheimer's disease progresses, the patient loses the ability to form short-term memories. Older-term memories remain intact for much longer.

In his book *Beating Alzheimer's: A Step Towards Unlocking the Mysteries of Brain Diseases*, Tom Warren<sup>10</sup> also describes his experiences with dementia. In June 1983, a computer-assisted tomography scan confirmed that Warren had Alzheimer's disease. His physicians gave him a maximum of 7 years to live. Yet nearly 4 years later, a new scan indicated that the disease process had reversed. Warren's self-treatment had included rectifying low hydrochloric stomach acid, the removal of all his teeth and mercury amalgam fragments from his gums, ethylene diamine tetracetic acid (EDTA) chelation therapy and high doses of vitamins and minerals. The latter included calcium, magnesium, and vitamins B3, B6, B12, and folic acid. According to Warren,<sup>11</sup> as a result of this regimen:

*My health, after several years, has so improved that I can say, in all honesty, that being able to feel good again has been worth all the pain and struggle. The road to recovery is not an easy path or a straight line, nor is it fast. Rather it is a cobblestone road of many tiny lifestyle changes, each another step toward renewed vitality and clarity of thought.*

## **SUMMARY**

At the core of both Blank and Warren's treatments was a reduction in exposure to metals, especially aluminum, and, in Warren's case, mercury. Chelation therapy also reduced body burdens of those toxins. Beyond this, diets were supplemented with extra minerals, particularly magnesium.

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*The acceptance of theories depends as much on the psychology of human beings as on the content of the theories. It is human beings who decide, individually and as a community, whether a theory indeed has explanatory power or provides understanding. This is why seemingly “extrascientific” factors such as productivity, portability, storytelling power and aesthetics matter. Sometimes it takes a long time (witness continental drift), but often the acceptance is immediate and intuitive – it fits. Like a nice sweater.*

Roald Hoffmann<sup>1</sup>

I know from sad experience that it is not easy to accurately predict the outcome of a horse race. If you consider only how fast each horse has run previously and bet on the one with the best times, you will probably identify the favourite, which wins only one race in three. Concentrating on class, the quality of the horses competed against in earlier races, will probably provide you with a fairly similar winning percentage. Running styles, track condition, jockey ability and nerve, legal and illegal drug use, equipment differences and failures, trainer skills, owner instructions (both good and bad), weather, the distance run, and horse health and mood all combine to affect the outcome of every race. That is why handicapping is so difficult, yet so much fun. Horse racing is a system that is influenced by a very large group of variables. As a consequence, even the most sophisticated computer programmes still have great difficulty in predicting winners with any reliable frequency. Perhaps



Alzheimer's disease is like that. Maybe many of the variables already discussed play small, but significant, roles in determining who will, and who will not, get the disorder.

In contrast, some systems have outcomes that are easy to predict from a few, or even one, key inputs. An atomic bomb is dropped and explodes. If you are at ground zero, or nearby, you will die. This is true for people within many miles of this location, whose injuries at greater distances may be affected by the type of building they are in at the time and the way the wind is blowing. There is no doubt, however, that the key input is the explosion of the weapon. Maybe Alzheimer's disease is similar. There may be one key, overriding variable that determines who does and doesn't get this form of dementia.

## **DOMINANT CAUSAL VARIABLE?**

### **Genetic**

One logical place to look for such a dominant causal variable would be amongst other forms of dementia. Do any of them, for example, provide a model that could be applied to Alzheimer's disease? There are some 70 different forms of dementia with a great variety of distinct triggers. Some, for example, like Huntington's disease,<sup>2</sup> are definitely of genetic origin. Huntington's chorea is an inherited, slowly progressive degenerative brain disorder that causes a loss of both mental faculties and physical control. Symptoms generally start to show up between ages 30 to 50 and progress for a 10 to 25 year period, increasingly affecting the individual's ability to think, speak, and move. Death eventually occurs due to heart failure, pneumonia, or some other complication. Approximately 1 person in 10,000 in the USA has Huntington's disease and over 200,000 more are at risk of inheriting it because one of their parents carries the

gene that is responsible.<sup>3</sup> There is no doubt that Huntington's disease is an autosomal dominant, inherited form of dementia linked to a single gene that codes for a mutated form of the protein, huntingtin. Although genetic testing can now predict who will develop the disease, there is no effective treatment. Unfortunately, every child of a parent with Huntington's disease has a 50 percent chance of subsequently developing it.<sup>4</sup>

Is it possible, then, that Alzheimer's disease also is simply genetic, the consequence of the miscoding of some protein? The major target for researchers into the genetics of late-onset Alzheimer's disease has been the APO E gene. This encodes for apolipoprotein which plays an important role in the movement and distribution of cholesterol for repairing nerve cells during early development and after any injury.<sup>5</sup> There are three major types of the APO E gene and considerable evidence suggests that the deposition of beta amyloid is greatest in those with APO E4 allele(s). This may be because one function of the APO E protein is thought to be the removal of beta amyloid. If this is the case, it is possible that the APO E4 variant does so less effectively than the other two APO E genetic types. Certainly, fewer beta amyloid deposits seem to occur in individuals with the APO E3 variant and even less of this protein is found in those with APO E2, which may even be protective.

Supporters of a major role for genetics in the genesis of Alzheimer's disease claim that, by age 85, people without the APO E4 allele have an estimated risk for developing this form of dementia of between 9 and 20 percent. In individuals with one copy of the gene the risk is thought to be between 25 and 60 percent, while in those carrying two copies of the APO E4 gene, the risk of developing Alzheimer's disease ranges from 50 to 90 percent.<sup>6</sup> However, those figures are clearly in error since in Maracaibo, Venezuela Alzheimer's disease is virtually unknown.<sup>7</sup> This must mean that globally, for people carrying two copies of

the APO E4 gene, the risk of developing Alzheimer's disease by age 85 ranges from 0 to 90 percent. In other words, the significance of the APO E4 gene is controlled by where you are, that is by location. Other lines of evidence support this position. Alzheimer's disease is extremely common in Norway.<sup>8</sup> However, even there, mortality from it varies dramatically from region to region. It is, for example, 15 times more common amongst males and 18 times more frequent in females in certain areas of Norway than it is in others. This country's population, however, is very homogeneous and these significant variations in death rates for Alzheimer's disease are extremely unlikely to be a reflection of an uneven distribution of the APO E4 allele in local inhabitants.<sup>9</sup> Another example of evidence for the role of location is found in northern Israel,<sup>10</sup> where all 821 elderly Arab residents of Wadi Ara were screened genetically because of the town's very high Alzheimer's disease prevalence rate. Surprisingly, the APO E4 gene frequency in this population was the lowest level ever recorded.<sup>11</sup> Taken as a whole, this evidence suggests that it is quite possible to develop Alzheimer's disease without even one copy of APO E4 allele and that some elderly people are never affected by this form of dementia, even if they have two copies of the APO E4 allele. This gene, therefore, may be important in Alzheimer's disease, but it is not a dominant causal variable.

## Pathogens

Dementia also can be caused by a variety of pathogens. For example, it occurs in the late stages of syphilis when the bacterium, *Treponema pallidum*, seriously damages the brain.<sup>12</sup> Similarly, dementia is seen in AIDS as HIV infection results in an extreme deficiency of tryptophan, leading to many of the symptoms of pellagra.<sup>13</sup> Dementia may also be the result of infection by abnormal prions, as observed in Kuru, and variant Creutzfeldt-Jakob disease (mad cow disease).<sup>14</sup> Prions are

misfolded proteins that have the unusual ability to induce normal proteins to also misfold, setting in motion a very slow chain reaction. Such misfolded prions are biologically inert, unable to participate in normal biological reactions and, as a consequence, tend to clump together forming plaques in the brains of patients with prion diseases, such as Kuru.

In their recent book, *Dying for a Hamburger: Modern Meat Processing and the Epidemic of Alzheimer's disease*, Waldman and Lamb<sup>15</sup> argue that Alzheimer's disease is probably caused by an as yet unidentified prion that has been widely spread by eating ground beef. While they provide some supporting evidence for this hypothesis, it seems very unlikely for several reasons. There is no feasible explanation, for example, why prions, viruses, bacteria, or other pathogens would be so much more likely to infect those who carry two copies of the APO E4 allele,<sup>16</sup> nor do Waldman and Lamb mention aluminum anywhere in their book so, of course, they make no attempt to explain why high fluoride and silicic acid might protect against prion infection, or why elevated monomeric aluminum might promote it.<sup>17</sup> In short, the idea that Alzheimer's disease is infectious is not backed up by any animal studies, nor does it account for the most convincing evidence summarized in the preceding chapters.

## **Toxins**

It has been known for centuries that mercury toxicity can cause dementia. In the 1850s, the descriptive phrase "mad as a hatter" was coined because of the many felters who became demented as a result of chronic mercury exposure during hat making.<sup>18</sup> Several other metals, including lead, bismuth, aluminum, and arsenic, are capable of badly damaging the brain.<sup>19</sup> As has been shown in the preceding literature survey, aluminum appears the most likely of these to be implicated in

Alzheimer's disease. Evidence was presented earlier in this book from Canada, Italy, England, Wales, and Norway that strongly suggests a role for aluminum in Alzheimer's disease. However, the relationship must be complex and exposure does not inevitably result in Alzheimer's disease. As previously pointed out, Maracaibo, Venezuela has a population of some 1,262,000 yet is virtually free of Alzheimer's disease.<sup>20</sup> Nevertheless, Maracaibo's drinking water has a mean aluminum content of 533 micrograms per litre, ranging from a minimum of 100 micrograms to a maximum of 2,060 micrograms per litre.<sup>21</sup> In short, Maracaibo's potable water aluminum levels are considerably higher than those acceptable by most international water quality standards and, indeed, frequently violate the maximum permitted by Venezuelan law.<sup>22</sup> Indeed, aluminum levels in Maracaibo's drinking water are higher than those found in most parts of Norway which suffer some of the highest Alzheimer's mortality rates on earth.<sup>23</sup>

## Trauma

The most obvious link between trauma and dementia occurs in many former boxers, who, during their fighting days, were hit repeatedly on the head. Such old sportsmen are often referred to as "punch drunks" because of dementia related to the brain damage caused by repeated blows.<sup>24</sup> The official name for the condition is pugilistic dementia. Primary and metastatic brain tumours also can damage the brain causing dementia. It has been discussed earlier that, in people with the APO E4 allele, severe head trauma often seems to initiate beta-amyloid deposition.<sup>25</sup> As a consequence, not surprisingly, if victims survive their injuries, such deposition reduces the time-of-onset of sporadic Alzheimer's disease in those genetically prone to it. This takes place, of course, because beta-amyloid is the major constituent of neuritic plaques. There seems to be no evidence that head trauma promotes this type of dementia in

those who do not carry the APO E4 allele. There must be more to Alzheimer's disease than trauma, therefore, whether brain injury is the result of physical force, tumour growth, or stroke.

### **Nutrient Deficiencies or Excesses**

The brain, like any other organ, requires a wide variety of nutrients, at specific levels, to prevent malfunction. It is recognized that deficiencies of vitamin B<sub>12</sub>, folate, and iron can result in reversible dementia.<sup>26</sup> Pellagra, for example, was a very rare disease when populations lived on diverse natural foods. When farmers began to grow cash crops, often concentrating on corn, many poor people in the southern USA and in Spain and Italy began to depend almost entirely on this grain. Unfortunately, corn is the ideal pellagra-producing food since it is low in tryptophan, vitamin B<sub>3</sub>, and isoleucine, yet contains elevated leucine. This combination results in deficiencies of tryptophan, and of vitamins B<sub>3</sub> and B<sub>6</sub>. As a consequence, the poor, who ate diets consisting of little more than corn, soon developed pellagra, characterized by the four Ds: dermatitis, diarrhea, dementia, and death.<sup>27</sup>

Dementia also can be caused by nutrient excess. Copper and manganese are both essential trace elements but excesses of either can result in dementia. Wilson's disease, for example, is a genetic disorder that promotes an excessive accumulation of copper in body organs. If unaddressed, it causes a wide variety of symptoms, including dementia and ultimately death. Fortunately, it is readily treated with the copper antagonist zinc and other medications.<sup>28</sup>

In Groote Eylandt, the largest island in the Gulf of Carpentaria, Australia, a neurological disease complex with upper motor-neuron and cerebellar signs has been identified in inhabitants with very high blood manganese levels.<sup>29</sup> Unfortunately, the

major settlement in Groote Eylandt is located very close to a large manganese mine. As a result, lumps of black manganese oxide can be picked up off the streets in Angurugu and a thin film of black dust can be wiped from furniture, cars, and other exposed objects. The local river, from which the water supply is derived, runs over a bed of manganese ore. It is not surprising then that “manganic madness” is common on the island.<sup>30</sup>

The evidence seen in the earlier literature review seems to suggest that calcium and magnesium deficiencies may be involved in Alzheimer’s disease.<sup>31-32</sup> Nevertheless, the fact that there is a strong genetic component and a well established aluminum link to the dementia clearly shows there is more to Alzheimer’s disease than simple deficiencies of these two bulk elements.

## **SUMMARY**

Almost anything that can seriously damage the brain can cause dementia, from the genetic abnormalities of Huntington’s chorea and Wilson’s disease to the repeated head blows of pugilistic dementia. In many cases the key causal variable is obvious. There is little doubt about the driving force of “manganic madness” or Kuru. Such dementias have a dominant trigger, such as a genetic abnormality or toxin. Other dementias, including Alzheimer’s disease, do not. They are more like a horse race than a bomb explosion. Clearly, neither being born with two copies of the APO E4 gene, nor drinking water containing high levels of aluminum or low concentrations of calcium and magnesium can, in and by itself, adequately explain global variations in the risk of developing Alzheimer’s disease. There must be several important causal variables involved in this form of dementia. The remainder of this book is devoted to identifying these variables and how they interact to raise, or lower, the probabilities of developing Alzheimer’s disease.

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*Cause and effect, means and ends, seed and fruit, cannot be severed; for the effect already blooms in the cause, the end preexists in the means, the fruit in the seed.*

Ralph Waldo Emerson: *Essay on Composition*

Clearly, there seems to be no single dominant causal variable in Alzheimer's disease. There is nothing unusual about this. Most chronic degenerative diseases occur as a result of interaction between a genetic aberration and a physical or social environment that magnifies its significance. This concept was described succinctly by Bishop and Waldholz<sup>1</sup> in their book *Genome*. These authors point out that "aberrant genes do not, in and of themselves, cause disease. By and large their impact on an individual's health is minimal until the person is plunged into a harmful environment." In short, the genetic aberration is only a weakness under certain circumstances. The key to the prevention and treatment of Alzheimer's disease, therefore, is not just the identification of the genetic variable(s) involved, but also an appreciation of which environments magnify and which diminish their significance.

### **APO E4: THE ABERRANT GENE**

The APO E4 gene is found in two-thirds of late-onset Alzheimer's disease patients in the USA, but it is not limited only to those with a family history of the disease. Nevertheless, having

even one copy of this allele seems to increase the risk of developing Alzheimer's disease by a factor of three when compared with the general population.<sup>2</sup>

It has been shown that the:

*effect of the ApoE4 gene seems to be dose-related, and not an autosomal dominant trait, which was previously assumed and observed from certain analyses. The presence of an ApoE4 gene lowers the age of onset for AD symptoms, while having two copies of the gene increases the chances for developing symptoms below the age of 70 by eight times, compared with someone who has copies of the ApoE3 gene. For those people with no copies of the ApoE4 gene, the average age of onset of AD is 85 years of age. The AD risk is increased because the age of onset is decreased. The possessing of an ApoE4 gene may speed up the AD process.<sup>3</sup>*

There can be little doubt, therefore, that the dominant aberrant gene involved in late-onset (sporadic) Alzheimer's disease is the APO E4 allele.<sup>4</sup> To grasp the genetic base of this type of dementia, it is essential to understand how this gene differs from other APO E isoforms. These biochemical differences have been described by Weisgraber.<sup>5</sup>

*ApoE is a 299-amino acid, single-chain protein with two structural domains that also define functional domains. The three common human isoforms, ApoE2, ApoE3, and ApoE4, differ at two positions in the molecule and have very different metabolic properties and effects on disease. ApoE3 (Cys-112, Arg-158) binds normally to low density lipoprotein (LDL) receptors and is associated with normal lipid metabolism, whereas ApoE2 (Cys-112, Cys-158) binds defectively to LDL receptors and, under certain circumstances, is associated with the genetic disorder type III hyperlipoproteinemia. ApoE4 (Arg-112, Arg-158) binds normally to LDL receptors but is associated with elevated cholesterol levels*

*and increased risk for cardiovascular disease. In addition ApoE4 is a major risk factor for Alzheimer's disease and predictor for poor outcome from head injury.*

It is clear from this description that the three common human forms of the APO E gene have distinct molecular structures and, as a consequence, different metabolic properties. The key question to be answered is, of course, "What is unique about the way the APO E4 isoform functions that encourages the growth of the plaques and neurofibrillary tangles that are so characteristic of Alzheimer's disease?". The answers to this query appear to be available in the literature. It would seem that beta-amyloid is normally soluble, but when the APO E4 protein latches on, it becomes insoluble and more likely to be deposited in plaques.<sup>6</sup> If this is correct, then people carrying the APO E4 allele have greater than usual difficulty in removing beta-amyloid from the brain and are, for genetic reasons, more likely to form plaques. It also has been established that there are "marked differences in the rates at which ApoE3 and ApoE4 bind to tau protein and also to a similar protein in dendrites. It is speculated that the ApoE4 product allows the microtubule structure to come undone, leading to the observed neurofibrillary tangles."<sup>7</sup>

It appears, therefore, that individuals who inherit the APO E4 allele(s) have greater difficulty than usual in removing brain beta-amyloid and tau. As a result, these proteins are accumulated more easily and those with the allele are more likely to develop Alzheimer's disease at an early age. The APO E4 allele also may be linked to even more neurological problems than this. To illustrate, animal experiments suggest that the "APO E3 gene is much more effective at promoting regrowth of nerve cell extensions after injury"<sup>8</sup> than is the APO E4 allele. APO E3 also may be more protective in preventing the loss of connections between neurons.<sup>9</sup> Beyond this, in cell cultures

APO E4 inhibits neurite outgrowth in rabbit dorsal root ganglion neurons.<sup>10</sup> Simply put, individuals with the APO E4 allele(s) are more likely to suffer from brain plaques and tangles and also probably are less capable of protecting against associated neuronal damage, or of recovering from it. That is, they are prime candidates for the development of Alzheimer's disease.

## **THE "HARMFUL ENVIRONMENT"**

The evidence seems overwhelming that the APO E4 allele is the key aberrant gene that increases the probability of developing late-onset (sporadic) Alzheimer's disease. If this is the case, what is the "harmful environment" that magnifies its impact?<sup>11</sup> The APO E4 allele reduces the ability to remove beta-amyloid and tau from the brain and to protect against any subsequent neuronal damage. As a consequence, the logical answer to this question would seem to be that any milieu that stimulates the production of beta-amyloid and tau will be most harmful to those carrying the APO E4 gene. This is because they will be the members of society who are the least able to prevent the deposition of brain neurofibrillary tangles and plaques caused by these proteins. Of course, if such environments are efficient enough at stimulating the formation of beta-amyloid and tau, they ultimately may promote Alzheimer's disease, even in those who carry APO E2 and APO E3 alleles. However, this is likely to occur less frequently and later in life because deposition will be slower.

Chapter 7 is a summary of what epidemiologists and geographers have learned about the impact of specific environments on the probability of the development of Alzheimer's disease in local populations. The strongest link, established by repeated statistical analyses, seems to be between chemical components

of drinking water and this form of dementia. Specifically, there is obviously a strong positive link between aluminum consumption, especially in its monomeric form, and the probability of locally elevated Alzheimer's disease incidence and mortality.<sup>12</sup> The negative health impact of aluminum, however, seems to be mitigated by silicic acid, calcium, and magnesium,<sup>13-14</sup> especially in potable water with a pH of between 7.85 and 8.05.<sup>15</sup> The impact of fluoride on Alzheimer's disease risk, however, seems to vary with acidity. The "harmful environment" for those who carry the APO E4 allele(s) would appear to be one in which drinking water is very acidic, and contains high levels of monomeric aluminum. Such threatening potable water also contains little or no silicic acid, calcium, or magnesium. The absence of the two latter bulk elements, of course, largely accounts for its softness and low alkalinity.

## **DANGEROUS WATERS**

Thus the epidemiological and geographical evidence allows us to identify the "harmful environments" for those carrying the APO E4 allele(s). What is needed now is an explanation of why such regions are so dangerous.

Consider first the apparently protective effects of silicic acid. Silica and aluminum are well known antagonists.<sup>16</sup> As a consequence, water rich in silicic acid is unlikely to carry much free aluminum. It seems likely also that aluminum's high affinity for silicon influences its absorption by the intestinal tract. This was demonstrated by a British clinical trial, conducted by Edwardson and coworkers,<sup>17</sup> in which volunteers were given an aluminum tracer (<sup>26</sup>A1) dissolved in orange juice. Elevated levels of this element were detected later in their blood. Six weeks later the same volunteers drank orange juice, again containing

aluminum but to which sodium silicate also had been added. After this second challenge, blood aluminum levels rose to only 15 percent of that previously reached in the absence of silica. Edwardson and colleagues<sup>18</sup> argued that the geographical association between Alzheimer's disease and the levels of aluminum in water supplies reflects this inverse relationship between aluminum and silicates. It is believed that silica promotes the formation of aluminosilicate species, limiting the gastrointestinal absorption of aluminum.

Aluminum also has a strong affinity for fluoride,<sup>19</sup> although the results are chemically complex because they vary with pH. In acidic water, fluoride and aluminum produce species such as  $AlF^{2+}$  but at a higher pH, the predominant form of aluminum created is  $Al(OH_4)$ . The significance of interactions between these two substances has been studied in some detail. Tennakone and Wickramanayake,<sup>20</sup> for example, have shown that the presence of only 1 ppm of fluoride in water adjusted with sodium bicarbonate or citric acid to pH 3, and boiled in an aluminum vessel, releases nearly 200 ppm aluminum in 10 minutes. Prolonged water boiling can elevate dissolved aluminum to 600 ppm. In contrast, if such water contains no fluoride, only 0.2 ppm aluminum levels are reached. In addition, in 10 minutes, 50 grams of acidic crushed tomatoes cooked in 200 ml of water containing 1 ppm fluoride produced a paste containing 150 ppm aluminum. In summary, acidic food or water, especially if fluoride is present, can leach excessive aluminum from cooking vessels. Furthermore, tea brewed in soft (acidic) water or flavoured with lemon juice contains significantly higher levels of bioavailable aluminum<sup>21-22</sup> than normal. These links between fluorine and aluminum may be of great significance in Alzheimer's disease since, in a recent study, Varner and co-workers<sup>23</sup> have demonstrated that the chronic administration of the fluoroaluminum complex ( $AlF_3$ ) to rats, in drinking water, resulted in elevated aluminum levels in brains and kidneys.

These high levels of aluminum were associated with damage to rat neuronal integrity, not seen in controls drinking double distilled deionized water. Interestingly, the epidemiologic and geographical evidence strongly suggests that in alkaline drinking water, fluoride is protective against Alzheimer's disease.<sup>24</sup> This implies that only those species created by aluminum and fluoride in acidic waters are dangerous to carriers of the APO E4 allele(s).

The solubility of aluminum, and probably the ease with which it is absorbed, vary markedly with pH, being lowest at about pH 6.5.<sup>25</sup> It is, therefore, quite soluble in both acidic and alkaline waters. However, the environmental evidence is very clear. Alzheimer's disease is common in regions where the water is acidic, yet relatively uncommon where the potable water is alkaline.<sup>26</sup> Taken as a whole, then, the epidemiological and geographical data shows that Alzheimer's disease incidence and mortality is highest in acidic environments which lack the protective effects of silicic acid. In contrast, they are depressed in populations drinking alkaline water that is elevated in silicic acid, calcium, magnesium, and fluoride. The most logical interpretation of this data seems to be that the harmful effects of aluminum, especially in its monomeric form, are greatest in individuals carrying the APO E4 gene when they are calcium and magnesium deficient.

The only missing link in the argument that Alzheimer's disease occurs most often in those carrying the APO E4 gene(s) who are exposed to monomeric aluminum is evidence showing that this toxin stimulates the overproduction of beta-amyloid and tau. If it does then the generation of these two proteins will cause the greatest difficulty to carriers of the APO E4 gene(s). In such individuals, beta-amyloid and tau will tend to accumulate most quickly, forming the plaques and neurofibrillary tangles that are characteristic of Alzheimer's disease. Evidence



is now presented to show that aluminum does, indeed, stimulate beta-amyloid and tau overproduction in individuals who are deficient in calcium and magnesium.

## **ALUMINUM, BETA-AMYLOID, AND NEURITIC PLAQUES**

The brains of Alzheimer's patients are characterized by neuritic plaques, which are composed of abnormal proteins. The cores of such plaques consist of beta-amyloid, a sticky snippet of a larger protein, amyloid precursor protein. It has been established that the beta-amyloid involved in such plaques is created when the brain is deficient in acetylcholine, a shortage that causes amyloid precursor protein to break down.<sup>27-28</sup> As was discussed previously, cholinergic neurotransmitter deficits are characteristic of Alzheimer's disease.<sup>29</sup> Indeed, a deficiency of acetylcholine is the basis for a recognized diagnostic test for this disorder.<sup>30</sup> This malfunctioning of the cholinergic system appears to be caused by aluminum's ability to inhibit the activities of the enzyme choline acetyltransferase,<sup>31-33</sup> a deficiency of which has been confirmed in Alzheimer's disease by several researchers including Perry,<sup>34</sup> Gottfries,<sup>35</sup> and Quirion and co-workers.<sup>36</sup> In addition, some neuritic plaques have been shown to contain acetylcholinesterase-beta amyloid protein complexes, further compromising the function of the cholinergic system.<sup>37</sup> Perry<sup>38</sup> has shown that in post-mortem Alzheimer's brain tissue there is an inverse relationship among the activities of choline acetyltransferase and acetylcholinesterase and senile plaque numbers. Furthermore, plaques containing acetylcholinesterase have higher resistance to low pH and anti-cholinesterase inhibitors and are more cytotoxic than normal plaques.<sup>39</sup>

The evidence, therefore, appears conclusive. Alzheimer's disease is commonest in populations that drink and bathe in acidic water that contains very little calcium, magnesium, or silicic

acid and elevated aluminum.<sup>40</sup> Under these circumstances, the risk of developing this form of dementia is highest in those members of the population who carry the APO E4 gene(s) because they are the least capable of removing beta-amyloid, a sticky, abnormal protein that is deposited in the brain as a result of aluminum's inhibition of the enzyme choline acetyltransferase, which is needed for the synthesis of acetylcholine. This beta-amyloid accumulates to form neuritic plaques.

## **ALUMINUM, TAU AND NEUROFIBRILLARY TANGLES**

Neurofibrillary tangles also are a characteristic of Alzheimer's brains. Such tangles consist mainly of an abnormal form of the protein tau which is highly and unusually phosphorylated.<sup>41</sup> Calcium/calmodulin kinase II acts as a catalyst in the phosphorylation of tau,<sup>42</sup> a process that is stimulated by two phospholipids,<sup>43</sup> phosphatidylserine, and phosphatidylethanolamine. However, aluminum interacts with calmodulin by displacing the calcium ion to form a stable Al-calmodulin complex.<sup>44-47</sup> Under these circumstances, calmodulin becomes less flexible, is prevented from reacting with several other proteins, and is inhibited in its regulatory functions. In addition, aluminum creates fatty acid abnormalities in the phospholipids, which normally stimulate the phosphorylation of tau.<sup>48-50</sup>

Beyond this, Yamamoto and colleagues<sup>51</sup> have shown that aluminum appears to inhibit the dephosphorylation of tau in the rat brain. It seems likely, therefore, that in the presence of elevated aluminum both phosphorylation and dephosphorylation of tau are disrupted, largely by the replacement of calcium by aluminum in calmodulin.

Furthermore, hemodialysis patients exposed to elevated aluminum develop depressed serum alkaline phosphatase levels.<sup>52</sup>

Abnormally low phosphatase concentrations also have been reported from the brains of Alzheimer's patients.<sup>53</sup> Aluminum-induced abnormalities in levels of phosphatases, enzymes required to remove phosphate groups from protein, also appear to be involved in the formation of neurofibrillary tangles. It appears that such an aluminum-induced lack of phosphatase,<sup>54</sup> in the brains of Alzheimer's patients, occurs because of an excess of phosphates in tau that prevent this protein from performing its normal role of securing vital parts of the neuronal cytoskeleton. Thus, the cell is harmed and hyperphosphorylated tau is precipitated to form tangles. According to Roushi,<sup>55</sup> animal studies suggest that such extra phosphates may cause neural damage even before tangles form, by interfering with one of tau's normal functions, assembling and stabilizing the microtubules that carry cell organelles, glycoproteins, and other vital substances through neurons.

It has been demonstrated that the more phosphate groups that are attached to synthetic neurofilament fragments, the easier it is for aluminum ions to bind and cross-link neurofilaments.<sup>56</sup> The presence of aluminum, therefore, appears to change the paired helical filaments that make up neurofibrillary tangles so they accumulate and are not removed, in the normal way, by protein-digesting enzymes. Interestingly, a laser microprobe study of the elemental content of neurofibrillary tangles in Alzheimer's disease, undertaken by Good and coworkers,<sup>57</sup> established that the only metallic elements found to be consistently present were aluminum and iron.

Evidence that aluminum can stimulate the accumulation of both beta-amyloid and tau proteins has been provided by Kawahara and coworkers.<sup>58</sup> The researchers investigated the neurotoxicity of aluminum by exposing cultured rat cerebral cortex neurons to aluminum chloride for in excess of 3 weeks. As a result, a degeneration of neuritic processes occurred,

accompanied by a build-up of both beta-amyloid and tau proteins. Aluminum, therefore, can stimulate the production, in the rat cerebral cortex, of the key components of both neuritic plaques and neurofibrillary tangles, diagnostic of Alzheimer's disease.

Again the evidence appears to be conclusive. Alzheimer's disease is most common in populations that use acidic drinking water that contains little or no silicic acid, calcium, or magnesium. Such potable water, however, often carries elevated aluminum.<sup>59</sup> Under these conditions, the risk of developing Alzheimer's disease is greatest amongst those members of the population who carry the APO E4 allele(s).<sup>60</sup> In part, this is due to the fact that they are the least capable of removing tau from the brain. Unfortunately, in such acid environments this abnormal protein is deposited more often because of the inhibition of the enzymes calcium/calmodulin kinase II and alkaline phosphatase by aluminum. This deposition gives rise to the neurofibrillary tangles that are a hallmark of Alzheimer's disease.

## **SUMMARY**

Individuals who inherit APO E4 gene(s) are less capable than the general population of removing the beta-amyloid and tau proteins that form the bulk of neuritic plaques and neurofibrillary tangles. As a result, such people are at higher risk of developing Alzheimer's disease in regions that promote the deposition of beta-amyloid and tau. Such "harmful environments" are those in which the potable water is acidic, high in monomeric aluminum, and lacks silicic acid, calcium, and magnesium. Under such circumstances, aluminum can enter the brain and impair the enzyme choline acetyltransferase, creating an acetylcholine deficiency. A shortage of acetylcholine encourages the

growth of senile plaques. Similarly, aluminum interferes with the enzymes calcium/calmodulin kinase II and alkaline phosphatase, promoting the formation of neurofibrillary tangles. Plaques and tangles created in this manner are the hallmarks of Alzheimer's disease. Such relationships, therefore, explain why this form of dementia is most common in regions of high water acidity, in those members of the population that carry the APO E4 isoform.

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## A BARRIER TO ANTAGONISM

*It all looks beautifully obvious – in the rear mirror. But there are situations where it needs great imaginative power, combined with disrespect for the traditional current of thought, to discover the obvious.*

Arthur Koestler<sup>1</sup>

### CROSSING THE BLOOD-BRAIN BARRIER

Science is very subjective and medicine even more so. Until the data supporting a new hypothesis are overwhelmingly persuasive, belief holds sway. This generalization is particularly true when a change in paradigm involves a serious loss of income. Apologists for aluminum, who oppose its neurotoxicity, have argued that the blood-brain barrier will prevent this metal impacting on the brain until after serious damage already has occurred from other causes.<sup>2-3</sup> This argument is incorrect. Yumoto and coworkers<sup>4</sup> injected the radioisotope <sup>26</sup>Al into healthy rats and demonstrated that a considerable amount of this aluminum isotope was incorporated into the cerebrum within 5 days after one injection and continued to show a gradual increase in the brain for a further 70 days. This accumulation of aluminum was accompanied by a decline in dendrites in cortical nerve cells and in attached spines. These changes implied a decrease in the amount of information that could be received. Many similarities have been reported from the brains of Alzheimer's patients.

Aluminum's ability to cross the blood-brain barrier is influenced by the form in which it is absorbed and the levels of other compounds in the blood. To illustrate, aluminum maltolate is absorbed easily by the intestinal tract. It seems also to be able to quickly cross the blood-brain barrier.<sup>5</sup> Furthermore, as it does, it increases the permeability of this barrier, a process with subsequent serious toxicity implications. That is, aluminum maltolate may affect the blood-brain barrier adversely, making it permeable to other damaging toxins. This may account for the variety of symptoms seen in subtypes of Alzheimer's disease and even in some other forms of dementia. Interestingly, Rao and coworkers<sup>6</sup> have suggested that maltolate-treated, elderly rabbits can be used as a good animal model of Alzheimer's disease, because of their neurofibrillary pathology.

In 2003, Kawahara and colleagues,<sup>7</sup> researchers from Tokyo's Metropolitan Institute for Neuroscience, described the application of aluminum maltolate to primary cultured neurons of the rat cerebral cortex, rat hippocampus, and to an immortalized hypothalamic neuronal cell line. They discovered that this form of aluminum was extremely toxic to neurons, causing rapid death. Aluminum acetylacetonate also was shown to have a similar ability to kill neurons.

Aluminum maltolate is not the only substance that can enhance aluminum's ability to cross the blood-brain barrier. To illustrate, Deloncle and coworkers<sup>8</sup> have shown that when there is an increase in sodium L-glutamate in whole blood, plasma aluminum penetrates red blood cells. This would suggest that aluminum crosses the erythrocyte membrane as a glutamate complex. Experiments with rats have shown that, similarly, aluminum can pass the blood-brain barrier as a glutamate complex and then be deposited in the cortex. This aluminum-L-glutamate complex is neurotoxic *in vivo*.<sup>9</sup> Nevertheless,

aluminum enters neurons and alone induces possible conformational changes in tau which are detected by the Alz-50 antibody. Aluminum combined with glutamate does not, and neither does glutamate alone.<sup>10</sup>

## **REACHING THE BRAIN**

In the preceding chapter it was argued that, on reaching the brain, aluminum apparently is able to inhibit enzymes such as choline acetyltransferase (needed for the synthesis of acetylcholine) and calmodulin (a catalyst involved in phosphorylation). The most likely explanation of this relationship is that aluminum is antagonistic with the cofactors of these, and probably many other, enzymes.

Enzymes are biological catalysts that speed up chemical reactions.<sup>11</sup> They bind temporarily to one or more of the reactants taking part in the reaction that they are catalysing. By doing this, enzymes reduce the amount of activation energy that is needed and, as a result, speed up the reaction. To illustrate, acetylcholinesterase (an enzyme that appears to play a key role in Alzheimer's disease) catalyses the breakdown of the neurotransmitter acetylcholine at various types of synapses and at the neuromuscular junction. This junction is a specialized synapse that triggers the contraction of the skeletal muscle. One molecule of acetylcholinesterase breaks down approximately 25,000 acetylcholine molecules every second, allowing the rapid "resetting" of the synapse for another nerve impulse transmission.<sup>12</sup> It is obvious, therefore, that if aluminum inhibits such reactions it is going to have a rapid, significant biochemical impact.

While most enzymes are proteins, they typically require an additional nonprotein cofactor before they can function.<sup>13</sup> Many

of the cofactors are ions of metallic elements such as zinc, copper, manganese, potassium, calcium, and magnesium. Others are small organic molecules called coenzymes. The B vitamins, thiamine (B<sub>1</sub>), riboflavin (B<sub>2</sub>), and nicotinamide (B<sub>3</sub>), for example, are precursors of such coenzymes.<sup>14</sup>

Enzymes are usually specific to the particular reactions that they catalyse and to the substrates that are involved in these reactions. That normally means that one enzyme cannot replace another, nor are cofactors usually interchangeable. It is clear, consequently, that bulk and trace elements are essential for the correct functioning of enzymes and for life. In a discussion of the roles played by metal ions in living cells, Kench<sup>15</sup> points out that they form a “cationic climate” in which all interactions occur. He further argues that in enzymatic processes there is a complex competition for sites on enzymes and substrates at the sub-cellular level. As a result, the preferential absorption of the ions of certain bulk or trace elements, or their antagonists, can either block or promote enzyme activity, altering the entire biochemistry of the cell. According to Kench:<sup>16</sup>

*Around all the macro-molecular structures in the living cell hovers a cloud of metal ions, jostling for position on the surface of the large molecules and according to their numbers and characters, in the case of enzymes, helping or hindering the movement of molecules – substrates or products – to and fro.*

The wealth of living forms is reflected at the cellular and sub-cellular level by a vast number of possible molecular inter-relationships, among which the relatively indestructible metal ions appear to have been exploited fully in a directive capacity, quickening or slowing the rate of structural change of the more evanescent carbon compounds, helping to provide these metabolic bridges and feeds-back.

It is at this level that the genetic and, hence, biochemical susceptibilities to “harmful environments” operates. It is hardly surprising that depressed calcium and magnesium intake, combined with abnormally high aluminum absorption, may inhibit some enzymatic processes. This is most likely to be true for those involving enzymes that have aluminum antagonists, such as calcium, magnesium, and iron, as cofactors.

## **ANTAGONISM**

Antagonism among elements is widely established. To illustrate, many diseases in livestock occur because fodder, enriched in particular minerals, results in shortages in others. Cobalt deficiencies, which cause wasting in sheep and cattle, for example, can usually be linked to a high iron and manganese soil content.<sup>17</sup>

Selenium is antagonistic with arsenic, cadmium, and mercury, relationships with major human health implications. Regions that experience elevated soil mercury levels are typically those that experience high cancer mortality rates. This is because, while selenium is very protective against many cancers, it combines easily with mercury to form mercury selenide. This compound is extremely insoluble and does not pass into the food chain. Crops and livestock produced in such high soil mercury areas, therefore, tend to be selenium deficient and so are associated with elevated cancer mortality.<sup>18</sup> Such antagonistic relationships between minerals are commonplace and appear to occur because ions with similar valence of electronic shell structures, or similar electronic configurations,<sup>19-22</sup> are antagonistic towards each other. Aluminum shows this type of antagonism towards divalent metals including zinc, phosphorus, calcium, and magnesium.<sup>23-26</sup> Aluminum’s biological activity is influenced further by at least two other elements, silicon

and fluorine, some compounds of which are able to chelate it while others promote its solubility. Dietary levels of minerals formed from these six elements greatly affect aluminum's absorption by the digestive tract and its ability to cross the blood-brain barrier. If it reaches the brain, the negative impact of aluminum again is due largely to its antagonism with calcium, magnesium, phosphorus, and zinc, since it has a strong tendency to replace them in important enzymes. The resulting novel compounds then create cascades of biochemical dysfunctions which eventually cause neuronal degeneration, ultimately culminating in Alzheimer's disease. Evidence for such antagonism already has been provided in the previous discussion of the inhibition of the enzymes choline acetyltransferase and calmodulin by aluminum and the role of these deactivations on the formation of plaques and neurofibrillary tangles.

## **SUMMARY**

The ability of aluminum to cross the blood-brain barrier is strongly influenced by the form in which it is absorbed and the levels of other compounds in the blood. Aluminum malto-late is particularly dangerous. On reaching the brain, aluminum interferes with those enzyme cofactors with which it is most antagonistic. These include calcium, magnesium, and probably zinc and phosphorous. Some of the enzymes involved, and the roles they play in the development of Alzheimer's disease, are discussed in detail in the following chapter.

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*Natural laws have no pity.*

Robert Heinlein<sup>1</sup>

The principle “Pluralitas non est ponenda sine neccesitate” or “plurality should not be posited without necessity” is often accredited to the medieval Franciscan monk William of Occam (ca. 1285-1349).<sup>2</sup> The concept is known as Occam’s razor, or the principle of parsimony, and is now interpreted to mean “don’t multiply hypotheses unnecessarily” or “the simpler the explanation the better.” More crudely, it has become “keep it simple, stupid.” Here, I interpret Occam’s razor to mean that the aluminum antagonist hypothesis is more likely to be correct if it can account, not just for the vulnerability caused by the APO E4 allele(s) and associated plaques and tangles, but also other pathological and biochemical abnormalities seen in Alzheimer’s disease. An attempt now is made to show that this is possible.

### **NUCLEUS BASALIS OF MEYNERT**

As previously described, certain neurons found at the base of the brain, known as the Nucleus Basalis of Meynert, appear to die in Alzheimer’s disease without any evidence of plaques or tangles.<sup>3</sup> Since these neurons produce acetylcholine, their death is not surprising. It is likely to occur because aluminum, as already shown while discussing the deposition of beta-amyloid and the development of neuritic plaques, can inhibit choline acetyltransferase.<sup>4-5</sup> Since this enzyme is essential for the

synthesis of acetylcholine, it is expected that neurons dedicated to acetylcholine production and distribution are affected very adversely by aluminum. Interestingly, as expected, this decrease in the metabolic activity in the nucleus basalis neurons in Alzheimer's disease is more common in patients with either one or two APO E4 allele(s).<sup>6</sup> The eventual death of nucleus basalis neurons in this type of dementia means that less than normal acetylcholine is available to the brain, reducing both memory and learning capacity.<sup>7</sup>

## **DEMYELINIZATION, RETROGENESIS, AND ALUMINUM**

As already discussed, because memory loss is so typical of Alzheimer's disease, most research has focussed on the brain's grey matter, especially on plaques and tangles. It is becoming clear, however, that myelin proteins, lipids, and cholesterol also are significantly affected in Alzheimer's disease. This process is known as demyelination and seems to play a key role in retrogenesis, the loss of the patient's abilities in the reverse order to which they developed during childhood and infancy.<sup>8</sup>

The key question to be answered here is "can retrogenesis be explained by aluminum antagonism?" Evidence, largely from animal studies, now will be presented to show that it can.

According to Raval-Fernandes and Rome:<sup>9</sup>

*Myelination is a multistep ordered process whereby Schwann cells in the peripheral nervous system (PNS) and oligodendrocytes in the central nervous system (CNS), produce and extend membranous processes that envelop axons. Mechanisms that regulate this complex process are not well understood. Advances in deciphering the regulatory components of myelination have been carried out primarily in the PNS and although the*

*mechanisms for triggering and directing myelination are not known, it is well established that myelination does not occur in the absence of axons or axon/neuron-derived factors. This appears to be true.*

Despite our incomplete knowledge of myelination, it is clear that aluminum disrupts the process. Deloncle and colleagues,<sup>10</sup> for example, did an ultrastructural study of the rat hippocampus in five distinct groups of rats. Three of these consisted of young animals, one group of which received daily subcutaneous injections of aluminum L-glutamate. The other two groups of young rats were injected with either sodium L-glutamate or saline solution. The two remaining rat groups consisted of older animals, one of which received subcutaneous aluminum L-glutamate on a daily basis. The other was untreated. The evidence collected showed that aluminum L-glutamate caused a thinning of the myelin sheath even in young rats. This breakdown in myelin did not occur in the young control group of sodium L-glutamate rats. It was seen, however, in the aluminum injected older rats where the myelin sheath was thinned to breaking point. Myelin loss also occurred, but less dramatically, in untreated elderly rats. It is clear from this experiment that aluminum accelerates myelin loss in rats, a process which occurs naturally but more slowly in elderly animals. A similar experiment was conducted by Golub and Tarara,<sup>11</sup> who fed Swiss-Webster mice diets containing aluminum lactate from conception to maturity, a period of 45 days. Mean myelin sheath widths on the spinal cord were found to be 16 percent less in the aluminum treated group than in the control group. Golub and Tarara<sup>12</sup> concluded that aluminum exposure can interfere with myelination of the spinal cord in mice.

Verstraeten and coworkers<sup>13</sup> have shown that because myelin has a high relative ratio of lipids to proteins compared to other membranes, it appears particularly susceptible to oxidative

damage promoted by aluminum. This is due to the high content of galactolipids found in myelin from aluminum intoxicated mice. These lipid abnormalities cause changes in membrane physical properties that seem to accelerate oxidation rates.<sup>14</sup>

These animal experiments clearly demonstrate that aluminum can alter the nature of myelin, accelerate its oxidation rates, and promote its rapid loss from the hippocampus and spinal cord. Exactly how these procedures occur is uncertain. In a study of brains from monkeys chronically administered aluminum, Sarin and colleagues<sup>15</sup> were able to show, however, that this metal had inhibited three membrane-bound enzymes: specifically  $\text{Na}^+\text{K}^+$  ATPase, acetylcholinesterase, and, most interestingly, the myelin-specific enzyme 2'3'-cyclic nucleotide phosphohydrolase.

Aluminum, therefore, interferes with myelin in numerous ways. It has the ability to inhibit three membrane-bound enzymes in the brain membranes of primates.<sup>16</sup> It can cause a rapid thinning of the myelin sheath in both rats<sup>17</sup> and mice,<sup>18</sup> and it can alter its composition by increasing galactolipids and so make myelin more prone to oxidation.<sup>19-20</sup> It does not seem much of a step to suggest that these destructive processes probably lie behind the demyelination and associated retrogenesis seen in Alzheimer's patients.<sup>21</sup>

## **ALUMINUM AND BRAIN CELL MEMBRANES**

There is something fundamentally wrong with cellular brain membranes in Alzheimer's patients. They display an abnormal viscosity; that is, they are unusually sticky. This seems to disrupt the activities of various enzymes, receptors, and membrane carriers and may be linked to dendritic spine loss.<sup>22</sup> These abnormalities appear related to irregularities in the biochemistry

of the phospholipids that concentrate in such brain cell membranes. Corrigan and coworkers,<sup>23</sup> for example, have shown that in Alzheimer's disease, phospholipids from the parahippocampal cortex, including phosphatidylcholine, phosphatidylserine, and phosphatidylinositol, contain below normal levels of alpha-linolenic acid. In addition to this depression of the level of n-3 polyunsaturated fatty acid, abnormalities also occur in levels of n-6 essential fatty acids. It has been demonstrated further that not only are the biochemical compositions of phospholipids from Alzheimer's patients abnormal but that total concentrations of such membrane phospholipids are low<sup>24</sup> and that their regional distribution in the brain is irregular.<sup>25</sup>

It has been suggested that the biochemical abnormalities seen in phospholipids in Alzheimer's disease are the result of elevated oxidative stress. However, aluminum also seems to be more directly involved. To illustrate, aluminum chloride has been shown to inhibit the incorporation of inositol into phospholipids.<sup>26</sup> Deleers and coworkers<sup>27</sup> also have demonstrated aluminum-induced lipid phase separation and fusion of phospholipid membranes. However, it seems more likely that disruption of phospholipase A2 by aluminum<sup>28</sup> is the primary cause of the biochemical abnormalities seen in phospholipids in Alzheimer's disease, and the chief cause of related brain membrane dysfunctions. Certainly, phospholipase A2 plays a key role in the metabolism of membrane phospholipids,<sup>29</sup> is decreased in Alzheimer's disease,<sup>30</sup> and is inhibited by aluminum chloride.<sup>31</sup>

## **ALUMINUM AND OXIDATIVE STRESS**

There is overwhelming evidence that Alzheimer's disease brain cells are subjected to elevated oxidative stress and that amyloid plaques are a focus of cellular and molecular oxidation.

Much of the destruction of neurons that characterizes Alzheimer's disease has been linked to the lipid peroxidation of cell membranes caused by free radicals. This process seems to occur because of disturbed defense mechanisms in Alzheimer's disease which are associated with a self-propagating cascade of neurodegeneration.<sup>32-33</sup> It has been established, for example, that Alzheimer's patients display depressed plasma antioxidant status associated with significantly low vitamin E levels.<sup>34</sup>

There is considerable evidence that aluminum itself reduces the body's defence against free radical damage. In dialysis patients, for example, serum glutathione-peroxidase levels are significantly depressed.<sup>35</sup> Similarly, animal studies have demonstrated that the oral administration of aluminum sulphate, especially in the presence of citric acid, inhibits brain superoxide dismutase and catalase activities.<sup>36</sup> Interestingly, vitamin E, which is depressed in Alzheimer's patients, can protect rats against associated aluminum-induced free radical damage.<sup>37</sup> Other evidence of the significance of oxidative stress includes a significant increase in erythrocyte Cu/Zn superoxide dismutase and catalase activity in the blood of Alzheimer's patients<sup>38</sup> and a pronounced increase in superoxide dismutase immunoreactivity in olfactory epithelium.<sup>39</sup>

Exactly how aluminum is involved in the catastrophic loss of neurons from free radical damage is being established by van Rensburg and coworkers<sup>40-41</sup> and Fu and colleagues.<sup>42</sup> The former have shown, for example, that both beta-amyloid and aluminum dose-dependently increase lipid peroxidation in platelet membranes. Their research has established that beta-amyloid is toxic to biological membranes and that aluminum is even more so.<sup>43</sup> Beyond this, van Rensburg and colleagues have demonstrated that iron encourages lipid peroxidation both by aluminum and by beta-amyloid protein. This is of considerable interest since only the metallic elements found in the

neurofibrillary tangles of Alzheimer's disease are aluminum and iron.<sup>44</sup> Van Rensburg and coworkers' in vitro model also demonstrated that melatonin prevented lipid peroxidation by aluminum and beta-amyloid protein in the absence of hydrogen peroxide. If the latter were present, melatonin could only slow the process.<sup>45</sup>

Fu and coworkers<sup>46</sup> have begun to explain how beta-amyloid specifically damages neurons. Their cell culture research has shown that beta-amyloid interferes with calcium homeostasis and induces apoptosis in neurons by oxidative stress. This latter process involves the catecholamines (norepinephrine, epinephrine, and dopamine), which increase the toxicity of beta-amyloid to cultured hippocampal neurons. These findings are consistent with the much earlier research of Hoffer, Osmond, and Smythies,<sup>47-48</sup> who argued that the oxidation of adrenalin to adrenochrome was responsible for the hallucinogenic symptoms seen in schizophrenia. More recently, Hoffer<sup>49</sup> has suggested that the oxidation of dopamine to dopachrome lies behind the psychotic symptoms seen in Parkinsonism, in many long-term levodopa users. Fu and coworkers<sup>50</sup> also have been able to show that the antioxidants vitamin E, glutathione, and propyl gallate can protect neurons against damage caused by amyloid beta-peptide and the catecholamines.

Aluminum also may increase free radical damage in Alzheimer's disease by inhibiting the protective copper/zinc metallo-enzyme, superoxide dismutase. Normally, this is one of the major enzymes that provides protection against free radicals. However, Shainkin-Kesterbaum and coworkers<sup>51</sup> showed that in vitro, at the levels of the enzyme found in dialysis patients, aluminum severely inhibited its protective effects. This inhibition of superoxide dismutase's antioxidant activity was directly proportional to the level of aluminum. Silicon was found to have a similar inhibitory effect on the enzyme. The disruptive



influence of aluminum on superoxide dismutase may account for the fact that, while zinc supplementation generally improves mental alertness in the elderly, in Alzheimer's patients it accelerates deterioration of cognition, encouraging amyloid plaque formation.<sup>52</sup> This may be due to the fact that, in the latter stages of Alzheimer's disease, it cannot be used in disrupted superoxide dismutase production and so merely stimulates free radical formation.

## **SUMMARY**

Aluminum does more than just cause the accumulation of the beta-amyloid and tau that disrupts the brains of Alzheimer's patients with neuritic plaques and neurofibrillary tangles. Its inhibition of choline acetyltransferase eventually kills the acetylcholine neurons in the Nucleus Basalis of Meynert. Beyond this, its negative impact on  $\text{Na}^+\text{K}^+$  ATPase, acetylcholinesterase, and on 2'3'-cyclic nucleotide phosphohydrolase appears responsible for the destruction of myelin and the associated retrogenesis that accompanies Alzheimer's disease. Aluminum also inhibits the enzyme phospholipase A2, probably causing brain membrane dysfunctions, and seems to cause depression of antioxidant status by reducing levels of brain glutathione peroxidase, superoxide dismutase, and catalase. As a result, the lipid peroxidation of cell membranes by free radicals is accelerated.

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*By the eighteenth century, the theorists had succeeded in obfuscating with a bewildering fog of shifting hypotheses a problem that should have been, and indeed was at one time, solved by basic observation and common sense. Physicians would have been better off throwing out everything they had learned and starting over with basic, observable truths. It would take a remarkably bright and original thinker to even begin to deconstruct the intricate latticework of preposterous ideas to uncover the small kernel of truth that lay underneath it all.*

S.R. Brown, *Scurvy*<sup>1</sup>

The evidence presented in this book so far strongly suggests that people who inherit APO E4 allele(s) are less capable than the general population of removing brain beta-amyloid and tau proteins. Consequently, such individuals are at higher risk of developing Alzheimer's disease, as these abnormal proteins build up and form neuritic plaques and neurofibrillary tangles. Naturally, this process occurs more often and most rapidly in regions that promote the deposition of beta-amyloid and tau. Such "harmful" environments are those where drinking water is acidic, high in monomeric aluminum, and lacking magnesium, calcium, and silicic acid. Under such circumstances, aluminum enters the brain and impairs various enzymes, including choline acetyltransferase, calcium/calmodulin kinase II, alkaline phosphatase, and phospholipase A2. The end result of this process is the abnormal brain pathology seen in Alzheimer's disease patients and the disrupted biochemistry

with which it is associated. In an earlier publication,<sup>2</sup> I called this explanation of the downward spiral, known as Alzheimer's disease, *Foster's Multiple Antagonist Hypothesis*.

The most effective way to test the validity of this hypothesis is to attempt to use it to explain the evidence that has been collected about Alzheimer's disease by disciplines as diverse as genetics and history. That is, to try to see whether the scattered pieces of the Alzheimer's disease jigsaw puzzle can be put together into a coherent picture, using the multiple antagonist hypothesis as a dominant theme. To assist in this process, Table 1 lists the clues identified in the preceding literature review chapters. For ease of identification, each clue is numbered according to the chapter in which it is first discussed and it is lettered to identify its position within that chapter. To illustrate, clue 1C (Demyelination) is the third clue discussed in Chapter 1 - *What Was I?*

What follows is my attempt to explain each of the clues in this table using the multiple antagonist hypothesis as a starting point. I cannot explain some of them. This may be because the multiple antagonist hypothesis is incorrect or incomplete, or the data the clue is based on was in error, or I am too ignorant to be aware of the real link between the tested hypothesis and the clue. My goal, therefore, is to explain the majority of the clues in Table 1 and to do so in a manner that is more convincing than explanations that have been put forward using all other competing hypotheses.

## **Table 1: The Pieces of the Jigsaw Puzzle**

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### Chapter 1. *Who Was I?*

- A. Retrogenesis involves loss of abilities in cognition, coordination, behaviour, language, and feeding in the reverse order they were acquired.
- B. Decline in neurologic reflexes, glucose metabolism, and EEG activity.
- C. Demyelination.
- D. Similarities of central nervous system decline seen in Alzheimer's disease, Guamanian amyotrophic lateral sclerosis, and Parkinsonism with dementia.
- E. Alzheimer's disease is more common in those with two copies of the APO E4 allele.

### Chapter 2. *In the Beginning: A History*

- A. Amyloid plaques.
- B. Neurofibrillary tangles.
- C. Dementia common in the elderly for hundreds of years.
- D. Dominant form of senile dementia varies spatially.
- E. Prevalence of Alzheimer's disease increasing.
- F. Age-adjusted Alzheimer's disease mortality probably rising in USA, Canada, England, and Norway.

### Chapter 3. *The Brain Drain: Pathology and Genetics*

- A. Beta amyloid precursor protein creates disproportionate beta-amyloid protein forming plaques.
- B. Abnormal tau creates tangles.
- C. Neurons producing acetylcholine die.
- D. Myelin protein, lipids, and cholesterol reduced.
- E. Early Onset Alzheimer's disease linked to genetic aberrations on chromosome 1, 14, and 21.
- F. Sporadic Alzheimer's disease higher in those with APO E4 allele.

### Chapter 4. *Putting the Disease in its Place*

- A. Great variation in incidence and prevalence of Alzheimer's disease at the local level.
- B. Alzheimer's disease virtually non-existent in Maracaibo, Venezuela.
- C. Alzheimer's disease exceptionally common in south and south eastern coastal areas of Norway.
- D. Migration alters incidence of Alzheimer's disease in ethnic groups of Japanese and African descent.



## Chapter 5. *Biochemical Anomalies*

- A. Longstanding glucose deficiencies in Alzheimer's patients.
- B. Abnormalities in cholinergic system.
- C. Tetrahydrobiopterin depressed.
- D. Dopamine, norepinephrine and serotonin levels low.
- E. Depressed glutamate levels.
- F. Elevated adenylate cyclase activity.
- G. Difficulties in absorbing calcium.
- H. Elevated brain aluminum.
- I. Depressed magnesium and potassium in the hippocampus.
- J. Tau is hyperphosphorylated.
- K. Neurofibrillary tangles contain copper, zinc and iron.
- L. Several other proteins abnormal.

## Chapter 6. *Other Risks, Further Hazards*

- A. Risk factors include hypertension.
- B. High ratio LDL to HDL cholesterol?
- C. Homocysteine elevated.
- D. Diet, sage, curcumin, vitamin E, B12 and folic acid, fish, nuts, fruits, vegetables protective.
- E. Smoking?
- F. depression.
- G. Severe head trauma.
- H. Stress.
- I. Osteoporosis (women only).
- J. Diabetes mellitus.
- K. Restricted education.
- L. Aging.

## Chapter 7. *Down to Earth: Location, Location, Location*

- A. High drinking water levels of monomeric aluminum.
- B. Aluminum additives in foods.
- C. High local aluminum levels in soils and sediments.
- D. Elevated drinking water pH and silica (silicic acid) protective.
- E. Drinking water fluoride protective in some situations.
- F. Calcium protective.
- G. Magnesium protective.
- H. pH of drinking water between 7.85 and 8.05 highly protective.
- I. Elevated where rainfall is acidic.

## Chapter 8. *Checking Out Alternatives*

- A. Beneficial herbs include: sage (*salvia lavandulaefolia*).
- B. Bacopa (*Bacopa monniera*).
- C. Ginkgo biloba.
- D. Lesser Periwinkle (*Vinca minor*), alkaloid Vinpocetine.
- E. *Hupezia serrata*, alkaloid Huperzine A.
- F. Galantamine.
- G. Lion's Mane mushroom (*Hericium erinaceum*).
- H. Beneficial minerals include: calcium and magnesium ascorbates.
- I. Lithium.
- J. Beneficial amino acid: acetyl-L-carnitine?
- K. Beneficial lipid: phosphatidylserine.

## Chapter 9. *Conventional Medical Wisdom*

- A. Cholinesterase inhibitors: donepezil (Aricept), tacrine (Cognex), Galantamine, rivastigmine, and metrifonate.
- B. N-methyl-D-aspartate receptor antagonist: memantine.
- C. Nonspecific drugs: estrogen, testosterone?
- D. Nonsteroidal anti-inflammatory drugs: aspirin, ibuprofen, indomethacin.
- E. Monoamine oxidase-B inhibitors: Selegiline (deprenyl).
- F. Vitamin E.

## Chapter 10. *Back from the Abyss*

- A. Avoiding aluminum cooking utensils and cans.
  - B. High magnesium diet.
  - C. Removal of mercury amalgam.
  - D. Ethyl diamine tetracetic acid (EDTA) chelation therapy.
  - E. High dose vitamins and minerals, including calcium, magnesium, and vitamins B3, B6, B12, and folic acid.
- 

## WHO WAS I?

This book's first chapter describes the current Alzheimer's disease pandemic and emphasizes its growing potential for future chaos. Three of the five major clues to the etiology of this dementia, retrogenesis, demyelination, and the APO E4 gene, have been accounted for already. Retrogenesis, for example,

occurs because aluminum inhibits at least three membrane-bound enzymes, Na<sup>+</sup>K<sup>+</sup> ATPase, acetylcholinesterase, and, most interestingly, the myelin-specific enzyme 2'3'-cyclic nucleotide phosphohydrolase.<sup>3</sup> As a result, it can cause rapid thinning of the myelin sheath<sup>4</sup> and increase its susceptibility to oxidative stress.<sup>5</sup> It seems very likely that these destructive processes cause demyelination and associated retrogenesis.

The APO E4 allele(s) frequently occur in Alzheimer's patients. This is because individuals inheriting this gene are inefficient in removing the beta-amyloid and tau proteins that form the bulk of the brain neuritic plaques and neurofibrillary tangles.<sup>6</sup> This gene is, therefore, a major handicap for those who are living in milieus and eating diets that promote the formation of beta-amyloid and tau. Such "harmful environments" are those in which drinking water is acidic, high in monomeric aluminum, and lacks silicic acid, calcium, and magnesium. Under these environmental conditions, especially if diet is dominated by processed foods that lack calcium and magnesium, aluminum enters the brain and impairs the enzymes choline acetyltransferase, calcium/calmodulin kinase II, and alkaline phosphatase, promoting the formation of plaques and tangles.<sup>7-8</sup> These are poorly removed by those who inherited the APO E4 allele(s).

There are similarities in the central nervous system decline in Alzheimer's disease, Guamanian amyotrophic lateral sclerosis, and Parkinsonism with dementia. The two latter disorders occur most frequently in Guam, the Kii Peninsula of Japan, and Western New Guinea. The river waters in such loci are exceptionally deficient in calcium and magnesium, suggesting that the intake of these minerals must be abnormally low in the local inhabitants.<sup>9-10</sup> In the Kii Peninsula, for example, potable water contains less than 2 ppm calcium and below 1 ppm magnesium.<sup>11</sup> Obviously, under such conditions, aluminum's ability to inhibit several enzymes is exacerbated.

Alzheimer's patients are very glucose deficient and seem to have been that way long before symptoms of this dementia become apparent. This glucose abnormality occurs, in part, due to aluminum binding with the phosphate enzyme, glucose-6-phosphate dehydrogenase and its interference with hexokinase.<sup>12</sup> To illustrate, Cho and Toshi<sup>13</sup> purified two isozymes from pig and human brains and showed that they contained an enzyme-aluminum complex. They were then able to show that glucose-6-phosphate could be completely inactivated by aluminum, but that this enzyme's potency could be restored by the three aluminum chelators: citrate, sodium fluoride, and apotransferrin. However, aluminum's negative impact on glucose metabolism is not limited to inhibiting the glucose-6-phosphate enzyme. Lai and Blass<sup>14</sup> have shown that this metal also inhibits hexokinase activity in the rat brain, but that high levels of magnesium can reverse this process. Aluminum also seems to inactivate hepatic phosphofructokinase, an important control site in the glycolytic pathway.<sup>15</sup> It is hardly surprising, therefore, that Alzheimer's disease patients display glucose abnormalities.

## **IN THE BEGINNING: A HISTORY**

It is very difficult to prove, with any certainty, that age-adjusted incidence and mortality from Alzheimer's disease has been rising since Dr. Alois Alzheimer first identified this dementia in Auguste D. This is due to the impact on the data of improved diagnosis, changes in public and physician education, altered attitudes towards Alzheimer's disease, changes in the coding and classification of dementias, and increases in life expectancy due to mitigation of other causes of death. As a result, while prevalence of Alzheimer's disease is clearly increasing rapidly as the population ages, it is less certain that the probability of a specific individual developing this type of dementia, at a given age, is also rising.

Scottish law permits a unique verdict. When the prosecutor is unable to provide conclusive evidence but the jury feels that the accused, nevertheless, is guilty as charged, it is able to bring down a verdict of “not proven.” My Scottish grandmother explained to me that this verdict meant “not guilty, but don’t do it again.”

This is how I feel about the history of Alzheimer’s disease. All the evidence points towards a steady increase in age-adjusted incidence and mortality, but such trends are very difficult to prove beyond a shadow of a doubt. In *Dying for a Hamburger*, Waldman and Lamb<sup>16</sup> examined the number of articles in the medical literature in the years since the initial identification of Alzheimer’s disease. From an ever rising interest in this form of dementia they concluded:

*Alzheimer’s disease has become more and more common – to the point that today the dementias of aging are considered the norm rather than the exception. But, as we will see, it was – even in fairly recent times – so rare that the greatest medical observers of all time did not even mention it.*

If one accepts that Waldman and Lamb<sup>17</sup> are correct about a steady increase in the incidence of Alzheimer’s disease, can the multiple antagonist hypothesis explain it? Obviously, such an increase cannot be due to any genetic cause. We do not have “epidemics” of genetic diseases, simply because the human genome does not change rapidly enough to trigger them. If, as the evidence strongly suggests, Alzheimer’s disease is becoming generally more common, it must be because the “harmful environments” that trigger it are now more widespread. As has been established, these are areas where potable water is acidic, high in monomeric aluminum, and lacking magnesium, calcium, and silicic acid. These environments are particularly dangerous if the local population is eating mineral depleted diets.

There is no doubt that, globally, soils and water are becoming more acidic and, as a consequence, aluminum more soluble. Throughout the 20<sup>th</sup> and early 21<sup>st</sup> centuries, as a result of expanding fossil fuel consumption, ever increasing quantities of sulphur and nitrogen were emitted into the atmosphere. Here they were converted into sulphuric and nitric acids, raising the acidity of subsequent precipitation.<sup>18</sup> Such acid rain has caused extensive damage to the environment at local, regional, and even global scales. It has been particularly problematic in northern and central Europe, eastern North America, and eastern China, where it has been associated with many health costs.<sup>19</sup>

Simultaneously, commercial fertilizers have been used with increasing frequency. These consist mainly of nitrogen, phosphorus, and potassium. Due to heavy crop yields, agricultural soils have been depleted of several minerals that are important for human health, including calcium and magnesium. To illustrate, Marier and colleagues,<sup>20</sup> in *Water Hardness, Human Health, and the Importance of Magnesium*, have pointed out how this mineral is becoming less and less common in the food we eat because of the fertilizers used in the “Green Revolution.” As early as 1974, Elmstrom and Fiskele<sup>21</sup> claimed:

*Magnesium deficiency is a frequently-occurring nutrient deficiency in the South-Eastern USA [and] is a frequently-developing problem on well-fertilized soils, [involving] an imbalance between Mg and Ca, or between Mg and K.*

Similar magnesium soil deficiencies have been reported for many other countries, including France, Germany, Denmark, and Canada.<sup>22</sup>

As previously discussed, processing and cooking also remove minerals from food, and packaging and canning often add aluminum to it. Consequently, most of the populations of the

Western World appear to be very magnesium and often calcium deficient.<sup>23-24</sup> Simply put, drinking water is becoming more acidic, and so aluminum is more soluble, foodstuffs contain fewer minerals as the result of commercial fertilizers, and many of the remaining minerals are removed by processing and cooking. We are creating more “harmful environments” that allow aluminum to reach the human brain where it inhibits crucial enzymes. If there has been no increase in the incidence of Alzheimer’s disease as a result of these environmental and social trends, then the multiple antagonist hypothesis must be incorrect. However, it should be pointed out that, in Norway, there is no doubt that Alzheimer’s disease is now common in those counties receiving the most acidic rainfall.<sup>25</sup> This is not surprising since the ancient Shield rocks of Scandinavia are naturally highly deficient in both calcium and magnesium.<sup>26</sup>

## **THE BRAIN DRAIN: PATHOLOGY AND GENETICS**

Animal experts<sup>27</sup> have demonstrated that aluminum can cause both beta-amyloid and tau buildup in the brain. Aluminum is likely to be implicated, therefore, in the formation of neuritic plaques and neurofibrillary tangles. Similarly, deaths of the neurons that produce acetylcholine in the Nucleus Basalis of Meynert occur because aluminum inhibits choline acetyltransferase.<sup>28-29</sup> This enzyme is essential for both the synthesis and distribution of acetylcholine. The damage caused to myelin by aluminum through its inhibition of the three membrane-bound enzymes; Na<sup>+</sup>K<sup>+</sup> ATPase, acetylcholinesterase, and, most interestingly, the myelin-specific 2’3’-cyclic nucleotide phosphohydrolase has been described previously.<sup>30</sup>

The APO E4 allele’s role in promoting Alzheimer’s disease, because of the inefficiency with which those possessing this

genetic aberration can remove beta-amyloid and tau, has been reviewed in detail.<sup>31</sup> Genetically, however, there is more to Alzheimer's disease than the APO E4 gene. In fact, there seem to be several such links. To date, four genes have been identified as playing a role in either early- or late-onset Alzheimer's: canning, presenilin-1, presenilin-2, and apolipoprotein E genes.<sup>32</sup> Workers have linked most of these variants to familial early-onset Alzheimer's, but the apolipoprotein E4 allele is a relatively common risk factor for developing late-onset Alzheimer's disease.<sup>33</sup>

Considerable progress has been made in the interpretation of the significance of such genetic variants. To illustrate, mutations in the presenilin-1 gene seem associated with increased superoxide production and greater vulnerability to amyloid beta peptide toxicity.<sup>34</sup> Interestingly, mutations in the presenilin genes, which are linked to more than 40 percent of all familial cases of Alzheimer's disease, cause enhanced production of an abnormal form of canning.<sup>35</sup> This protein is longer than normal, aggregates more rapidly, kills neurons in culture more effectively, and precipitates preferentially to form amyloid plaques. The same elongated protein also is produced as a result of mutations in the gene encoding canning.

The literature suggests, therefore, that the gene variants that predispose to both early- and late-onset Alzheimer's disease do so because they either increase susceptibility to, or mimic, the aluminum-related degenerative processes previously described. That is, the genetic mutations involved in promoting the development of Alzheimer's disease duplicate some of aluminum's deleterious impacts on the brain and in so doing, encourage at least one of the following: the growth of neuritic plaques or neurofibrillary tangles, excessive free radical formation, and higher neural oxidative stress. As a result, unfortunate individuals carrying any one of the genetic variants are much more



likely to develop Alzheimer's disease, even if they are not exposed to the aluminum excess or vitamin and mineral deficiencies, that are normally associated with its etiology.

## PUTTING THE DISEASE IN ITS PLACE

On May 26, 2004, *The Scientist*<sup>36</sup> reported that the National Institutes of Health (NIH) was considering undertaking the largest population-based study ever carried out in the USA. The NIH had already been collecting information from researchers on the types of questions such a project should address. Its aim is to identify the gene-environment interactions involved in common human diseases. According to Terri Manolio,<sup>37</sup> director of the National Heart, Lung and Blood Institute's epidemiology and biometry program, a project like this is "the logical next step beyond the mapping of the human genome and doing case studies." In short, the US federal government is considering carrying out a survey of a representative sample of the US population that is likely to include as many as 500,000 participants from all geographic, racial, ethnic, and socioeconomic groups, as defined in the most recent US census.<sup>38</sup>

This politically correct idea involves collecting information on diet, lifestyle, and geographic area that might identify the environmental triggers that "switch on" genetic aberrations, so increasing the probability of developing a particular disease. Such a massive study would be very expensive and totally unnecessary. There are far easier, quicker, and cheaper methods of identifying the "harmful environments" that can exacerbate the negative effects of aberrant genes. In a letter to *The Lancet*, published in 1987, I pointed out that analyses of mortality data showed that in both the USA and Canada, death from diabetes mellitus increased where environmental magnesium and calcium levels were low, that is in soft water regions.<sup>39</sup> I suggested

also that diabetics would benefit from magnesium supplements. In early 2004, researchers from the Harvard Medical School came to almost the same conclusion after studying the dietary habits of 85,060 women and 42,872 men, for 18 and 12 years respectively, and determining who developed diabetes. Such a study, supported by the National Institutes of Health and National Institutes of Diabetes and Digestive and Kidney Diseases probably cost tens of millions of dollars and was completed almost 20 years after my own research was published.

Geographical evidence that can identify the triggers for genetic aberrations is readily available, generally free, and simple to analyse. Using it, one can locate the spatial extremes of any disease's incidence and mortality. These I term "hot spots," where the disease is particularly common and lethal, and "cold spots," where it is extremely rare or even unknown. These environmental extremes and their characteristics have been determined for numerous common illnesses. Consider, for example, the "cold spot" for osteoporosis.<sup>40</sup>

The ranchers of Texas are well aware that migration can alter bone strength and density. Cattle raised on the high plains of Deaf Smith County are larger and heavier than those from elsewhere in Texas.<sup>41</sup> Indeed, fully grown 6-year old cattle moved onto pasture in the high plains will gain a minimum of 250 pounds as their bones increase in size and weight. The skeletons of residents of Deaf Smith County are similarly dense and highly mineralized. The elderly there rarely show signs of demineralization and osteomalacia which are so common in other mature Texans. Cortices of their long bones are about one-half greater in thickness than those seen in Dallas County. In Deaf Smith County, the bones of residents 80 years or older only break as a result of severe trauma and then heal rapidly without pins or supports. In contrast, bones of the elderly of Dallas County often break as a result of demineralization and

then heal only with great difficulty. It is obvious from these observations that, in cattle, migration can greatly affect bone formation and that the environmental factors that promote it also affect humans in the same manner. The key to reducing the impact of osteoporosis, therefore, lies in the soils and water supply of Deaf Smith County, Texas, a “cold spot” for this disease.<sup>42</sup>

Each genetic aberration linked with a chronic disease has its own specific triggering (“hot spots”) and protective (“cold spots”) environments. Two hospital-based studies<sup>43</sup> involving brain autopsies of every patient dying with dementia in Maracaibo, Venezuela, a city with a population of 650,000, discovered only one Alzheimer’s case in over a decade. In contrast, in the worst affected Norwegian municipalities, during the period 1974-1983, the median annual age-adjusted Alzheimer’s disease mortality rates were between 44-55 per 100,000 for males and 87-109 per 100,000 for females.<sup>44</sup> These figures suggest that Alzheimer’s disease is at least 1,000 times more common in the municipalities along the south and southeastern coasts of Norway than in Maracaibo, Venezuela. Even within Norway itself, Alzheimer’s mortality was higher by a factor of 15 in some municipalities than in others, during this period.

The “hottest spots” for Alzheimer’s disease, therefore, appear to occur in the acidic, aluminum-enriched, calcium and magnesium deficient municipalities of southern Norway. This is exactly what the multiple antagonist hypothesis would predict. In contrast, the key to reversing the global Alzheimer’s disease pandemic lies in Maracaibo, Venezuela. Here even those with the genetic aberrations that are normally invariably associated with early-onset Alzheimer’s disease are not developing this form of dementia. Whether this is because of an aluminum antagonist in the water supply or herb, spice, or some other food or additive commonly eaten in Maracaibo is unknown.

We do not need a giant, time wasting population-based study of the genetic-environmental links in Alzheimer's disease. What is required is a detailed examination of the drinking water and diets of this Maracaibo "cold spot."

Naturally, the migration of any ethnic group from a "cold spot" to a "hot spot" or from either of these to a more neutral environment is likely to change its Alzheimer's disease incidence and mortality rates. This is especially true if the migration is associated with significant dietary change. This probably accounts for the rise in Alzheimer's disease seen in immigrants to the USA from Japan and Nigeria.<sup>45-46</sup>

## **BIOCHEMICAL ABNORMALITIES**

It appears as if, in individuals who have a depressed calcium and magnesium intake combined with abnormally high aluminum absorption, some enzymatic processes are inhibited. This inhibition is most likely to occur in enzymes that have aluminum antagonists, such as calcium, magnesium, and iron, as cofactors. It is not surprising, then, that since the end result of such enzyme inhibition is Alzheimer's disease, patients with this form of dementia experience a wide variety of biochemical abnormalities, some of which appear in Table 2. The longstanding glucose deficiencies seen in Alzheimer's patients, for example, are probably caused by aluminum's inhibition of glucose-6-phosphate dehydrogenase<sup>47</sup> and its interference with the hexokinase.<sup>48</sup> Abnormalities in the cholinergic system seem to be linked to aluminum's ability to inhibit choline acetyltransferase.<sup>49-50</sup> A depression of tetrahydrobiopterin, which is required for the synthesis of the neurotransmitters dopamine, norepinephrine, and serotonin, also occurs in Alzheimer's disease patients. This deficiency and its associated repercussions appear linked to aluminum's inhibition of the enzyme

dihydropteridine reductase,<sup>51</sup> which is essential for the maintenance of tetrahydrobiopterine.

The depressed glutamate levels seen in Alzheimer's disease may reflect the inhibition of brain glutamate decarboxylase activity<sup>52</sup> and the impairment of the glutamate-nitric oxide-cyclic GMP pathway in neurons.<sup>53</sup> Adenylate cyclase is a catecholamine sensitive enzyme that plays a major role in parathyroid hormone secretion. Its levels are elevated in Alzheimer's patients.<sup>54</sup> This seems to be because aluminum can cause an irreversible activation of adenylate cyclase, that Ebstein and colleagues have suggested may account for some of the neurotoxicity of that metal.<sup>55</sup> Similarly, the multiple antagonist hypothesis can account for the hyperphosphorylation of tau which appears linked to aluminum's ability to inhibit the dephosphorylation of this protein.<sup>56</sup> Indeed, in the presence of elevated aluminum, both the phosphorylation and dephosphorylation of tau are disrupted, largely by the replacement of calcium by aluminum in calmodulin<sup>57</sup> (Table 2).

**Table 2: Alzheimer's Disease and Aluminum: An Overview**

<i>Aluminum Impaired Enzyme</i>	<i>Consequence</i>	<i>Potential Treatment</i>
Glucose-6-phosphate dehydrogenase	Glucose metabolism impaired	Calcium, magnesium, citrate, sodium fluoride, apotransferrin
Hexokinase	Glucose metabolism impaired	Calcium, magnesium
Phosphofructokinase	Glucose metabolism impaired	Calcium, magnesium
Choline acetyltransferase	Acetylcholine deficiency Malfunction of cholinergic neurons Formation of senile plaques	Vitamin B <sub>12</sub> , m[zinc], estrogen, folic acid, calcium, magnesium phosphatidylcholine, lecithin, acetyl-L-carnitine
Adenylate cyclase	Elevated parathyroid activity	Magnesium
Dihydropteridine reductase	Depressed dopamine, norepinephrine and serotonin	Desferrioxamine, magnesium, copper, zinc, iron, calcium
Glutamate decarboxylase	Reduction in glutamatergic neurotransmission	Calcium, magnesium
Calcium/calmodulin Kinase II	Loss of calmodulin flexibility; formation of neurofibrillary tangles	Desferrioxamine, calcium, magnesium
Alkaline phosphatase	Neurofibrillary tangles	Calcium, magnesium
Phospholipase A2	Abnormal brain cell membranes	n-3 and n-6 essential fatty acids, calcium, magnesium, phosphatidylserine, phosphatidylcholine, phosphatidyl ethanolamine, phosphatidylinoditol
Na <sup>+</sup> K <sup>+</sup> ATPase	Abnormal cell membranes Demyelination?	
2'3'-cyclic nucleotide phosphohydrolase	Demyelination Retrogenesis?	

No claim is made that this enzyme list is complete. It almost certainly is not.

There are many enzymes that have calcium, magnesium, and other minerals or cofactors. It is quite possible that under certain deficiency conditions, aluminum can inhibit almost any of these. Two things are clear. So many inhibited enzymes have been identified, aluminum must be causing a very wide range of biochemical abnormalities in Alzheimer's disease patients. It is also clear that no pharmaceutical aimed at correcting the malfunction of a specific enzyme is ever going to be effective in the prevention and reversal of Alzheimer's disease. The only logical approach to preventing the disease is to block aluminum's access to the body, while simultaneously preventing mineral deficiencies.

## **OTHER RISKS, FURTHER HAZARDS**

Any model that seeks to explain Alzheimer's disease must be able to account for the established risk factors described in Chapter 6. An attempt will now be made to do this for the multiple antagonist hypothesis.

### **(1) Hypertension**

It comes as no surprise that hypertension is a risk factor for Alzheimer's disease. After all, both of these disorders are promoted by calcium and magnesium deficiency.<sup>58-60</sup> Naturally, therefore, they tend to occur together in the same people. Many individuals who have hypertension have developed it because they are deficient in calcium and magnesium, a condition that also increases their vulnerability to Alzheimer's disease.

### **(2) Cholesterol**

Cholesterol promotes the production and accumulation of beta amyloid protein.<sup>61</sup> In animal studies, it has been shown that

this process occurs more slowly if rabbits are given distilled, rather than tap water.<sup>62</sup> Such studies also have demonstrated that aluminum chloride increases plasma cholesterol levels in the rat, while simultaneously inhibiting numerous enzymes and decreasing plasma total lipids.<sup>63</sup> Exactly how aluminum elevates plasma cholesterol is, as yet, unclear to this author, but it does.

### **(3) Homocysteine**

High plasma homocysteine levels are also known to be a risk factor in Alzheimer's disease.<sup>64</sup> The Framingham study, for example, established that the higher the homocysteine level when first measured in elderly people, the more likely they were to become demented later in life.<sup>65</sup> Interestingly, Gottfries and coworkers<sup>66</sup> have shown that in the early stages of Alzheimer's disease, elevated serum homocysteine is a sensitive marker for cognitive impairment. Alzheimer's patients are choline deficient, probably because of aluminum's ability to inhibit the activities of the enzyme acetyltransferase.<sup>67-68</sup> Choline deficiency raises homocysteine levels by altering the metabolism of methionine<sup>69-70</sup> and would, as a result, account for both homocysteine's presence at high levels in the serum of those most at risk for Alzheimer's disease and the associated cognitive impairment that follows.

### **(4) Diet**

As previously described, a diet rich in fish, nuts, fruits, and vegetables is linked to a lower risk of developing Alzheimer's disease.<sup>71</sup> This is hardly surprising since nuts, fruits, and vegetables are usually good sources of calcium and magnesium,<sup>72</sup> thus mitigating the enzyme-inhibiting impacts of aluminum. Furthermore, Durlach and colleagues<sup>73</sup> have suggested that, in humans, vitamin E, selenium, magnesium, and other anti-



oxidants can protect against the deleterious metabolic consequences of apolipoprotein E4-4. In addition, cold water fish are typically elevated in the Omega 3 polyunsaturated fatty acids that are involved in maintaining brain structure.<sup>74-75</sup>

## **(5) Smoking**

Smoking is a lethal habit, but whether or not Alzheimer's disease is promoted by it is uncertain. It may well be one more disease laid at tobacco's door, since smoking decreases calcium absorption in the intestines and so promotes bone loss.<sup>76</sup> For reasons that are unclear, smokers exacerbate the problems this causes by choosing to eat diets that are lower in both calcium and vitamin D than those eaten by non-smokers.<sup>77</sup> These deficiencies tend to be corrected in ex-smokers, 5 years or more after stopping the habit.

## **(6) Depression**

There are many reasons depression may be an early indicator of increased risk of developing Alzheimer's disease.<sup>78</sup> It has been shown, for example, that aluminum inhibits glucose-6-phosphate dehydrogenase<sup>79</sup> and hexokinase.<sup>80</sup> The inhibition of these two enzymes seems to be associated with a longstanding glucose deficiency in Alzheimer's patients. There also appears to be a link between low glucose levels and depression. Patients with hypoglycemia, or low blood sugar, exhibit higher depression scores than those with normal blood sugar levels.<sup>81</sup> Since potential Alzheimer's patients have lower blood sugar levels, they are more likely to test positively for depression. Dialysis patients, exposed to highly elevated aluminum, suffered severe depression of their serum glutathione peroxidase levels.<sup>82</sup> This seleno-enzyme plays a major role in protecting against oxidative stress. Changes in selenium concentration in blood and brain have also been noted in Alzheimer's disease

patients.<sup>83</sup> It has been established further by five studies that selenium deficiency is a significant cause of depression in many people who do not have Alzheimer's disease and will probably never develop it.<sup>84</sup> It appears, therefore, that aluminum lowers brain selenium levels in individuals who will ultimately have Alzheimer's disease, and when it does they exhibit signs of depression.

## **(7) Severe Head Trauma**

The most likely reason those who survive severe head trauma appear more apt to subsequently develop Alzheimer's disease has been proposed by Nicoll and coworkers.<sup>85</sup> Individuals carrying the APO E4 allele(s) produce more beta-amyloid when they suffer head injuries. Consequently, if they survive the trauma, this deposition reduces the time-of-onset of sporadic Alzheimer's disease in those genetically prone to it, because, of course, beta-amyloid is the major constituent of neuritic plaques.

## **(8) Stress**

The Religious Orders Study that is evaluating aging in Catholic nuns, priests, and brothers has identified stress as a risk factor for Alzheimer's disease.<sup>86</sup> Although medical interest in stress can be traced back to Hippocrates,<sup>87</sup> it was not until the 1920s that physiologist Walter Cannon<sup>88</sup> showed that emotion-arousing incidents trigger an outpouring of epinephrine (adrenaline), norepinephrine (noradrenaline), and cortisol. During stress, the sympathetic nervous system increases respiration and heart rate, diverts blood to skeletal muscles, and releases fat from storage. All such changes prepare the body for what Cannon called "Fight or Flight," and are obviously part of a response system that has evolved in an effort to deal with perceived threats.

In the modern world, fighting or running away from problems are often impossible solutions. The result of chronic stress is overexposure to adrenaline, noradrenaline, and cortisol. These can lead to nervous disorders ranging from high blood pressure to depression,<sup>89</sup> both of which have already been linked to Alzheimer's disease. Beyond this, stress promotes free radical damage, a characteristic of Alzheimer's disease.

## **(9) Osteoporosis**

The probable link between Alzheimer's disease and osteoporosis<sup>90</sup> is hardly surprising. It is clear from the published literature that aluminum can promote extensive bone loss. In addition, both Alzheimer's disease and osteoporosis are more common in individuals who are deficient in calcium and magnesium.<sup>91</sup> Naturally, therefore, these disorders tend to occur together in the same person.<sup>92</sup>

There is no doubt that aluminum can cause bone loss. During the 1970s, a number of patients undergoing dialysis treatment, with tap water containing aluminum from treatment plants, developed osteomalacia, a disorder involving a softening of the bones resulting from impaired mineralization. This problem was recorded in Europe, North America, and Australia. In Great Britain, a survey of 1,293 patients in 18 centres established a very strong statistical relationship between bone softening and the aluminum content of the water supply used in dialysis.<sup>93</sup> This disorder was particularly common in Glasgow, Leeds, Newcastle, Plymouth, and Oxford, where drinking water aluminum levels were elevated.

To explore the relationship between bone strength and aluminum content further, Mjöberg<sup>94</sup> carried out 20 bone biopsies on patients who had not experienced dialysis, but who had suffered hip fractures. The aluminum and calcium content of

sampled materials established that there was no significant relationship between bone aluminum and gender or fracture type, but there was a statistically significant tendency towards higher aluminum levels in the bones of younger hip fracture patients. In general, therefore, while more research is necessary, Mjöberg's<sup>95</sup> results tend to support the hypothesis that aluminum impairs bone mineralization and increases fracture rates in the general population.

The use of water containing high levels of aluminum in the treatment of renal patients was also associated with significant increases in dialysis encephalopathy, a degenerative disorder of the brain that showed some similarities with Alzheimer's disease. Parkinson and colleagues<sup>96</sup> showed in Newcastle, for example, that none of the 10 patients in their twenties on home dialysis survived for 2 years. All died of dialysis encephalopathy, osteomalacia, or unexplained cardiorespiratory failure.

Beyond the dialysis evidence, aluminum has been linked to bone loss in Chinese villagers eating corn contaminated with mud and coal that were elevated in aluminum and fluoride.<sup>97</sup> Interestingly, such villagers experienced an extremely high urinary calcium loss, associated with both osteoporosis and osteosclerosis. The literature also contains a description of an 8-month-old boy suffering metabolic bone disease due to chronic aluminum-containing antacid use.<sup>98</sup>

Both osteoporosis and Alzheimer's disease occur frequently in individuals who are exposed to high levels of aluminum while simultaneously being calcium and magnesium deficient. It is not surprising, therefore, that the former is a predictor of the latter. Exactly how aluminum causes bone loss is not completely clear, but it appears to be due to its ability to cause an irreversible activation of adenylate cyclase, so stimulating the production of parathyroid hormone.<sup>99</sup> Aluminum absorption

is enhanced in the presence of abnormally high circulating parathyroid hormone and is preferentially deposited in both the bone and brain.<sup>100</sup>

## **(10)Diabetes mellitus**

Diabetes mellitus is a disorder that, like Alzheimer's disease, is common in those who live in magnesium deficient environments,<sup>101-102</sup> especially if they eat diets that are deficient in this mineral.<sup>103-104</sup> Like Alzheimer's disease, diabetes mellitus also involves glucose abnormalities. Aluminum interferes with the normal function of at least three enzymes, glucose-6-phosphate dehydrogenase,<sup>105</sup> hexokinase,<sup>106</sup> and phosphofructokinase.<sup>107</sup> These impacts cause glucose abnormalities in future Alzheimer's disease patients long before any cognitive deficits are seen. It seems likely, therefore, that similar enzyme inhibition plays a role in diabetes mellitus type II, accounting for its identification as a risk factor for Alzheimer's disease. Naturally, the impact of aluminum will be worse in those who are calcium and magnesium deficient.<sup>108</sup>

## **(11)Restricted Education**

Beyond the possibility that less educated individuals may be more likely to eat inappropriate diets, there appear to be three hypotheses that may explain why lack of education might increase the risk of developing Alzheimer's disease.<sup>109</sup> Firstly, it is possible that the APO E4 allele(s) that predisposes a significant section of the population to late-onset Alzheimer's disease might somehow also adversely affect an individual's ability to cope with the demands of an education. There seems, however, to be no available evidence to support this hypothesis.

Secondly, education might stimulate the brain's development, and thus increase its ability to withstand more degenerative

damage before Alzheimer's symptoms become apparent. There is certainly growing evidence that stimulation affects brain development. To illustrate, Rosenzweig<sup>110</sup> demonstrated that the number of neurons in the brains of rats was influenced by the stimuli in their environment. Rats that grew up in an "enriched" milieu were found to have more neurons in the cerebral cortex than those that did not. In addition, a rat from an "enriched" environment had a heavier cortex with thicker cortical coverings. Brain enzymes were also elevated. Globus<sup>111</sup> further discovered that such "enriched" environments increased the number of dendritic spines in the rat brain. Perhaps, as Restak<sup>112</sup> muses, learning, memory, and other brain functions in humans may depend to a large degree on the quality of environmental stimulation.

A third hypothesis that may account for the apparent link between lack of education and the risk of developing Alzheimer's disease would focus on exposure to toxic metals and inadequate dietary mineral intake. If a child was exposed to elevated aluminum while their calcium, magnesium, zinc, and phosphorous intakes were depressed, they might be unable to handle the rigours of higher education. Ultimately, these imbalances might also result in the development of Alzheimer's disease. There is clearly this type of negative relationship between lead exposure and depressed childhood intelligence.<sup>113</sup> Furthermore, Varner and coworkers<sup>114</sup> have shown recently that the chronic administration of drinking water containing aluminum-fluoride or sodium-fluoride to rats causes significant deficits in neuronal integrity that show regional brain differences. It has been established also that elevated hair aluminum levels seem to be associated with classroom withdrawal by young children.<sup>115</sup> Much of this aluminum may come from cans, but it should be noted that aluminum concentrations in most formulas derived from cow's milk are 10- to 20-fold greater than in human breast milk, and they are 100-fold greater in soy-based formulas.<sup>116</sup>

Deficiencies in trace and bulk elements also seem to adversely affect school performance. To illustrate, Marlowe and Palmer<sup>117</sup> compared 26 hair trace elements in two sets of young Appalachian children: an economically disadvantaged group of 106 from Head Start programs and 56 control group children from more prosperous backgrounds. Developmental disabilities, including communication and behavioural disorders, were noted in 13 members of the Head Start group, but were absent from the control group. Hair analysis also established that the mean levels of calcium, magnesium, and zinc were significantly depressed in children from the economically disadvantaged group. Conversely, Benton<sup>118</sup> reviewed five studies that suggested that vitamin/mineral supplements improved many children's performances during intelligence tests. To summarize, the evidence suggests that many children are exposed to excess aluminum, while being simultaneously mineral deficient. Such individuals appear to experience schooling difficulties early in life and may possibly develop Alzheimer's disease when older. This may be particularly true if they eat a high fat diet.<sup>119</sup>

## **(12) Aging and Increased Prevalence**

The human brain has comparatively little ability to repair itself. As a consequence, aluminum's damage tends to be cumulative, thus increasing the likelihood of developing Alzheimer's disease later in life. However, there seem to be other factors that increase the prevalence of this form of dementia in the elderly. As the individual ages, intestinal absorptive capacity is reduced, resulting in a decrease in calcium absorption. In addition, kidney function declines, and along with it there is a corresponding reduction in the production of active vitamin D, further decreasing calcium absorption in the intestines.<sup>120</sup> These changes typically lead to a loss of bone calcium and, as has been discussed previously, make aluminum absorption easier.

Not only is the aluminum burden of the brain likely to increase with aging in this way, but its ability to protect itself also characteristically declines. Hypovitaminosis, for example, is common in the elderly,<sup>121</sup> who are all too frequently deficient in antioxidants and are, therefore, more prone to oxidative stress. Beyond this, two hormones that decline with age, melatonin and estrogen, play roles in protecting the brain from aluminum. As their levels fall, damage from this element inevitably increases. The aluminum-estrogen association probably explains why, as Cohen<sup>122</sup> pointed out, Alzheimer's disease is more common in women than in men, a gender bias that cannot be explained entirely by the greater longevity of females.

## **DOWN TO EARTH: LOCATION, LOCATION, LOCATION**

The global geography of Alzheimer's disease appears to confirm the multiple antagonist hypothesis. Aluminum inhibits a wide variety of enzymes when its access to the brain is facilitated by acidity, combined with deficiencies of calcium, magnesium, and silicic acid. This is why certain environments increase the risks associated with the APO E4 allele(s) while others mitigate them. The world's highest known Alzheimer's disease mortality rates occur in southern Norway.<sup>123</sup> This is because the region's drinking water is being made highly acidic by polluted rainfall, lacks calcium and magnesium because of the local geology, and contains high levels of aluminum.<sup>124</sup> Under such conditions, aluminum, especially in its simplest monomeric form, can easily reach the brain and inhibit a wide variety of enzymes by replacing these normal cofactors. The brain malfunctions that follow are known as Alzheimer's disease and occur most rapidly in those carrying the APO E4 allele(s) because they are the least capable of repairing the associated damage.<sup>125</sup>



## CHECKING OUT ALTERNATIVES

Alternative medicine is a mixture of both the wisdom of the ages and the fads of the day. In some ways, it is ahead of conventional medicine, in others it is centuries behind. The gullible accept all of its protocols, the closed-minded, none. In reality, every alternative treatment needs assessing against the available evidence, so that the wheat and the chaff can be separated.

Chapter eight describes seven herbs or herbal extracts, three minerals, one amino acid, and one lipid that are now used regularly in alternative medicine to treat Alzheimer's disease. More logically, these can be divided into five classes, each of which tackles the disorder in a distinct way.

Lithium, calcium, and magnesium, especially in ascorbate forms, appear capable of significantly reducing aluminum's ability to reach the brain.<sup>126</sup> They probably also stop or slow aluminum's inhibition of brain enzymes. Bacopa (*Bacopa monniera*), Ginkgo biloba, and vinpocetine help to protect against the oxidative stress apparent in Alzheimer's disease. In contrast, sage (*salvia lavandulaefolia*), Huperzine A, and Galantamine are all capable of inhibiting the enzyme acetylcholinesterase, which breaks down the neurotransmitter acetylcholine. They may, therefore, help to slow the decline in acetylcholine and the associated memory loss that is a characteristic of Alzheimer's disease. In contrast, the Lion's Mane mushroom (*Hericium erinaceum*) seems to be a potent inducer of brain tissue regeneration that could be of great value to Alzheimer's patients. The lipid, phosphatidylserine, however, stimulates the cerebral metabolic rate for glucose which is always low in Alzheimer's patients because aluminum is inhibiting at least three glucose-related enzymes; specifically glucose-6-phosphate dehydrogenase, hexokinase, and hepatic

phosphofructokinase. All the necessary references to support these claims are given in chapter eight.

## **CONVENTIONAL MEDICAL WISDOM**

There is no conflict between the conventional medical treatment for Alzheimer's disease and the multiple antagonist hypothesis. In alternative medicine, sage, Huperzine A, and Galantamine, all herbs or their extracts, are used to treat this form of dementia. These medications all inhibit the enzyme acetylcholinesterase, which breaks down the acetylcholine, a deficit of which is associated with memory loss. Two very widely used conventional drugs, donepezil (Aricept) and tacrine (Cognex), do the same thing. So, too, do the cholinesterase inhibitors rivastigmine and metrifonate. It will be recalled that the acetylcholine deficiency, being addressed by these conventional treatments, is linked to aluminum's inhibition of enzymes of the cholinergic system, including choline acetyltransferase, and subsequent destruction of the acetylcholine-producing neurons in the Nucleus Basalis of Meynert.<sup>127</sup>

In contrast, memantine is designed to protect against the excitotoxicity of low brain glutamate concentrations. It has been argued previously that the imbalance of glutamate seen in Alzheimer's disease is a result of aluminum's inhibition of the glutamate decarboxylase<sup>128</sup> and impairment of the glutamate-nitric oxide-cyclic GMP pathway in neurons.<sup>129</sup> Nonsteroidal anti-inflammatory drugs, such as aspirin, ibuprofen, and indomethacin, may be useful in treating Alzheimer's disease since they reduce the damage caused by the build-up of beta-amyloid.<sup>130</sup> The latter, of course, is promoted by aluminum.<sup>131</sup>

Conventional medicine also accepts the use of Selegiline (deptenyl) and vitamin E as methods of reducing the widespread

oxidative stress seen in Alzheimer's disease. It was argued earlier, of course, that this results, in part, from aluminum's increase of lipid peroxidation.<sup>132</sup>

## BACK FROM THE ABYSS

Both Louis Blank<sup>133</sup> and Tom Warren<sup>134</sup> recovered from Alzheimer's disease after reducing their exposure to metals, especially aluminum and, in Warren's case, mercury. Chelation therapy also reduced body burdens of such toxins. Beyond this, their diets were supplemented with extra minerals, particularly magnesium. These steps are exactly what would be needed if the multiple antagonist hypothesis were correct.

## SUMMARY

In his book, *Science is God*, Horrobin<sup>135</sup> claims that:

*A good hypothesis has three major characteristics. It accounts for those facts in a precise, direct way. It makes predictions which are amenable to experimental testing and which suggests the direction in which further progress may be made.*

I feel sure that the evidence provided to this point in "What Really Causes Alzheimer's disease" has shown that Foster's Multiple Antagonist Hypothesis can account for the known facts about this type of dementia in a precise, direct way. Indeed, I would like to challenge those with a vested interest in promoting the use of aluminum to explain the observations in Tables 1 and 2 in a more convincing manner. What remains, then, is to demonstrate how progress in the prevention and treatment of Alzheimer's disease can be made by the application of the multiple antagonist hypothesis.

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*“Before I draw nearer to that stone to which you point,” said Scrooge, “answer me one question. Are these the shadows of the things that Will be, or are they the shadows of the things that May be only?” Still the Ghost pointed downward to the grave by which it stood. “Men’s courses will foreshadow certain ends, to which, if persevered in, they must lead,” said Scrooge. “But if the courses be departed from, the ends will change. Say it is thus with what you show me!”*

Charles Dickens, *A Christmas Carol*

While I was writing this, the final chapter of “What Really Causes Alzheimer’s disease,” the news media reported the death of former US President Ronald Reagan. This event took place on June 5<sup>th</sup>, 2004, when America’s only movie star president died of pneumonia complicated by Alzheimer’s disease.<sup>1</sup> Ronald Reagan had suffered from dementia for 10 years and had been the world’s most famous Alzheimer’s disease patient.

Aluminum inhibits a wide variety of enzymes. Those people who carry the APO E4 allele(s) have the greatest susceptibility to these disruptions and so develop Alzheimer’s disease more easily. Aluminum, especially in its monomeric form, is highly toxic in acidic environments that are deficient in calcium, magnesium, and silicic acid. From a scientific point of view, all of these risk factors, with the exception of genetic inheritance, are relatively simple to mitigate. Therefore, Alzheimer’s disease, in theory, is easily avoidable. There is no need for a

pandemic, or the \$100 billion annual loss that it degenerates in the USA alone.

Unfortunately, several major lobbies are likely to consider that a global Alzheimer's disease pandemic is an acceptable cost of doing business. If you doubt this, I suggest that you read *When Smoke Ran Like Water* by Devra David<sup>2</sup> and *The Fluoride Deception* by Christopher Bryson.<sup>3</sup> Remember them when you next read a statement that claims "the idea that aluminum has anything to do with Alzheimer's disease is an old, disproven theory." I am dedicating this chapter on strategies for reducing Alzheimer's disease incidence to former US president Ronald Reagan in the hope that those who honoured him may have the political power and drive to ensure that he did not suffer in vain.

I am, however, a realist. That is why June 5<sup>th</sup>, 2004 was also the day on which I bet on Birdstone (34/1) to beat Smarty Jones (1/5) in the Belmont Stakes. Therefore, I am including in this chapter a series of steps that any individual can take to help protect themselves against Alzheimer's disease. These can be used in the likely event that pressure groups continue to place profits ahead of health.

## **REDUCING SOCIETAL RISK**

### **Water Supply**

Exposure to acidic water that contains elevated aluminum and depressed calcium, magnesium, and silicic acid appears to promote Alzheimer's disease. One might naively expect that it would be a relatively simple matter to pass legislation reducing levels of aluminum in, and promoting the addition of calcium, magnesium, and perhaps silicic acid to, drinking water.

It would seem to be in the best interest of every government to save the billions of dollars spent in caring for Alzheimer's disease victims. Unfortunately, little in politics is so logical.

In August 1997, Paul W. Mason,<sup>4</sup> owner, operator, and proprietor of Adobe Springs, a mineral spring (which contains 110 mg/litre of magnesium), near San Jose, California filed suit against Donna Shalala, US Secretary of Health and Human Services, and Dr. Michael Friedman, Acting Commissioner of the US Food and Drug Administration. This case, No. C-97-20686 was heard in the United States District Court, Northern District of California. The plaintiff, Mason,<sup>5</sup> charged that for 77 years the US Food and Drug Administration had forbidden any health claims to be made for mineral water and that this, and other activities, had deliberately driven thousands of mineral water companies out of business. As a result of US Food and Drug Administration policies, therefore, the magnesium content of the average bottle of American water was, at the time of the case, 2.7 mg per litre. That is, bottled water produced in the USA contained very little magnesium. In contrast, similar products bottled outside the country carried, on average, 28 mg per litre of magnesium. That is, they contained over 10 times as much .

Mason<sup>6</sup> provided numerous scientific citations demonstrating that, for a wide variety of illnesses, incidence and mortality decrease as magnesium intake rises. From such evidence, he estimated that the US Food and Drug Administration's actions in promoting the use of magnesium-deficient water had resulted in the deaths of about 215,000 Americans each year, roughly one every 2.5 minutes. In total, this is more than the combined death toll of Americans killed in every war the country has fought, including the Civil War. Mason hoped that by filing such a suit he had provided the opportunity to argue the merits of increasing the magnesium content of the drinking



water of the USA. The case was dismissed quickly by Federal Judge Jeremy Fogel.<sup>7</sup> He essentially ruled that, although the magnesium-deficiency deaths caused by Food and Drug Administration policies may have exceeded those of the Holocaust, the matter was political rather than judicial. Indeed, Mason<sup>8</sup> was chastised for comparing the number of magnesium-deficiency caused deaths with those of the Holocaust, even though the totals appear similar. As far as I am aware, there have been no improvements in US Food and Drug Administration regulations. If this is so, Americans are still dying at the rate of roughly one every 2.5 minutes from government-promoted drinking water magnesium deficiency.<sup>9</sup> Unfortunately, former president Ronald Reagan may have been one of these victims. Mason and his wife have not given up. They continue their battle for better quality drinking water through locations that include *The Magnesium Web Site*<sup>10</sup> and that of the *Arab Healthy Water Association*.<sup>11</sup>

Not only do governments show little interest in increasing the magnesium content of drinking water, they routinely allow the use of aluminum sulfate as a flocculant by water treatment plants. This reduces the amount of sediment in the water supply, but greatly increases levels of dissolved aluminum, especially if the water is acidic.<sup>12</sup> Clearly, aluminum sulfate must be replaced by alternatives. Its use probably explains why Alzheimer's disease is so common in western Wales, amongst the elderly who were exposed for many years to this practice.<sup>13-14</sup>

## **Foods**

The adoption of the western diet has been associated with major changes in the incidences of many illnesses.<sup>15</sup> Mortality from infection tends to decline significantly, only to be replaced by chronic, degenerative diseases, including heart disease,

cancer, and diabetes mellitus.<sup>16</sup> Such western illnesses appear to have as their root cause the consumption of highly refined foods that are low in minerals and fibre but contain elevated sugar, salt, animal protein, and saturated fats.<sup>17-18</sup> Support for this idea can be drawn from the global geographical distribution of such chronic degenerative diseases, their emergence in native populations that migrate to industrialized societies, and the lower mortalities for such diseases experienced by vegetarians, including the Seventh-Day Adventists, even though they live in the Developed World.<sup>19</sup>

The western diet promotes Alzheimer's disease in three distinct ways. Firstly, it tends to be deficient in calcium and magnesium,<sup>20</sup> making those who eat it very susceptible to aluminum toxicity. Secondly, many foods are canned, wrapped, and/or cooked in aluminum. The more acid the food, the more easily it appears to dissolve this metal. Thirdly, maltol is added to many processed foods in an attempt to "improve" flavour.<sup>21</sup> There can be little doubt that the typical western diet is too low in many minerals.<sup>22</sup> Consider, for example, magnesium. This occurs at relatively high levels in unrefined whole grain cereals and in green leafy vegetables, nuts, seeds, lentils, beans, and peas.<sup>23</sup> However, farmers do not routinely add magnesium to soils, so its levels are often relatively depleted in their crops. Since it is fairly soluble, processing and cooking also often can greatly reduce magnesium levels in foods. To illustrate, the milling of whole grain lowers the magnesium content to only 20 percent of that initially present. Processing further reduces it, so that while one slice of whole wheat bread provides 24 mg of magnesium, a slice of white bread contains only 6 mg.<sup>24</sup>

For these reasons, dietary intake of magnesium has been declining for at least 100 years in the USA, falling from about 500 mg to 175-225 mg per day. The average daily intake is now about 228 mg in both American and British women.<sup>25</sup> These

levels are far too low – only two-thirds of the US Recommended Daily Amount, which is, in itself, not adequate.<sup>26</sup> Simply put, the western diet is deficient in magnesium, increasing susceptibility to a wide range of illnesses, including Alzheimer’s disease. If the government is truly interested in promoting better health, it must pass legislation that encourages the addition of both calcium and magnesium to widely consumed foods and to drinking water in regions where this is acidic. Silicic acid might also be a very beneficial additive to drinking water. It would be valuable to increase the use of calcium and magnesium-enriched fertilizers in regions where soil pH is low.

Wrapping, canning, and cooking food in aluminum also needs to be addressed. At the very least, standards could be set to minimize the leaching of aluminum into the beverages that are drunk on a massive scale by children. Beyond this, it is imperative that the use of maltol to enhance food flavour be prohibited. It may be remembered that this additive greatly increases the ability of aluminum to cross the blood-brain barrier.<sup>27</sup> Indeed, when researchers want to study a rabbit whose brain has been badly damaged by Alzheimer’s-like plaques and tangles they feed maltol to it.<sup>28</sup> There is no logical reason why maltol should be allowed to be routinely added to hot chocolate, beer, and some commercially baked goods and many other products.

## **REDUCING PERSONAL RISK: THE PAUL REVERE APPROACH**

During all but the very recent past, individuals have been responsible for their own safety. In disaster planning, this reliance on personal observation and action, supported by the “wisdom” of legends, folktales, and experience, has been called the Paul Revere approach.<sup>29</sup> Such self-reliance, in both disaster planning and health care, has been very largely superceded,

in the Developed World, by government responsibility for safety and public health. Much of the power for the detection of threats and the maintenance of public health now rests with the operators of sophisticated technology, such as satellites, radar, medical equipment, and computer systems, which are beyond the control and often the understanding of the general public. Power now rests with experts whose prestige and wealth largely depends on paradigms that support the Establishment. In short, the scientific elite, to which we have given the responsibility for maintaining health and avoiding disasters, is not going to bite the hand that feeds it. There is much more to be gained from the search than from the discovery, and out of treatment than cure. This is especially true when prevention threatens the interests of powerful industrial lobbies. For these reasons, I do not expect to see government restrictions on monomeric aluminum levels in drinking water. Nor is it likely that elevated pH levels, or the widespread addition of calcium, magnesium, or silicic acid to potable water will be encouraged. Despite the obvious threat it poses to the human brain, the food industry lobby will probably prove capable of preventing a maltol ban. Products “enriched” with this flavour-enhancer are likely to continue to fill supermarket shelves. Nevertheless, there are numerous steps that individuals can take to reduce their own chances of developing Alzheimer’s disease, if they choose to take the Paul Revere approach to this illness.

### **Avoidance of Aluminum**

For most of those reading this book, the average day will begin with a shower. If the water used is acidic and deficient in calcium and magnesium, it is possible that it will be a source of aluminum that enters the body through the pores and nose. This exposure to aluminum is most likely if the water supplier uses aluminum sulfate as a flocculant to remove sediment.

Once dried off, most readers will smear their bodies with a layer of aluminum provided by antiperspirants and deodorants.<sup>30</sup> How much of this aluminum passes through the skin into the body is unclear, but McGrath<sup>31</sup> has argued that underarm shaving and frequent use of antiperspirants and deodorants seem linked to an early age of breast cancer diagnosis. British researchers<sup>32-33</sup> provided evidence to support the feasibility of McGrath's hypothesis, reporting traces of parabens in every tissue sample taken from 20 different breast tumors. Parabens are chemicals used in deodorants and other cosmetics that can mimic estrogen. The hormone estrogen is known to encourage breast tumor growth. Clearly, parabens can enter the body from deodorants and it is possible that aluminum can do the same. Deodorants with a herbal base do not usually contain these toxins.

Then comes breakfast. Tea, coffee, hot chocolate are usually made with water from the tap. It is important not to use soft, acidic water which is likely to contain monomeric aluminum. Most water supply companies will provide chemical analyses, allowing the assessment of the aluminum, calcium and magnesium content of their product. If not, private companies can conduct such analyses relatively cheaply. If colas or fruit juices are drunk, they are likely to have come from cans. These are typically made of aluminum. The longer the drink has been in the can, the higher the aluminum levels in it are likely to be.<sup>34</sup> In addition to any aluminum it contains, hot chocolate is likely to be "enhanced" with maltol, so increasing the likelihood that this metal will reach the brain. Similarly, tea brewed in acidic water or flavoured with lemon juice contains significantly higher levels of bioavailable aluminum than normal.<sup>35</sup>

### **Increasing Calcium and Magnesium**

After breakfast comes lunch, dinner and a variety of snacks. Junk food, because it is so heavily processed, is usually a very

poor source of minerals, including calcium and magnesium. As previously pointed out, the average British and North American diet contains less than half the calcium and magnesium required to avoid the associated deficiency illnesses, including Alzheimer's disease. The best way to address this problem is to eat many of the mineral enriched foods listed in Table 3. These include salmon, sardines, broccoli, spinach, and bok choy, for example, which are all high in calcium.<sup>36-37</sup> Pumpkin seeds, almonds, Brazil nuts, and whole grain brown rice are good sources of magnesium.<sup>38</sup>

Certain supplements, especially mineral ascorbates, provide high levels of both calcium and magnesium. Alacer Corporation, Foothill Ranch, California, a company with which I have no financial associations, provides excellent mineral ascorbate products. One tablet of Super-Gram II, for example, contains 4 percent of calcium and 8 percent of magnesium recommended daily allowance. Emer'gen-C is a fizzing drink mix that is pleasant to take when added to water. It provides 1,000 mg of vitamin C and 32 mineral complexes, including calcium and magnesium. Alacer's products were used in the joint Russian-Committee on World Health research projects that produced a marked reversal of memory loss in the elderly.<sup>39-41</sup>

**Table 3: Examples of Foods Usually Elevated in Magnesium and/or Calcium**

	<i>Magnesium</i>	<i>Calcium</i>
NUTS	Almonds Brazil Nuts Cashews Hazelnuts Peanuts Pumpkin Seeds	Almonds Brazil Nuts Hazelnuts Sunflower Seeds
VEGETABLES	Black eyed peas Swiss Chard Collards Kohlrabi Green Peas Spinach Turnip Greens Yams	Black beans Bok Choy Broccoli Collards Kale Pinto beans Spinach Turnip Greens
MEATS	Flanksteak (Beef) Ground Beef (lean) Round Steak (Beef) Ham Venison Goose	Flanksteak (Beef) Rabbit Chili con carne (with beans)
SEAFOOD	Cod Crab Flat fish Haddock Mackerel Oysters Shrimp Snapper	Agar-agar Carp Crab Hijiki Kombu Oysters Salmon Sardines Shrimp Wakame
GRAINS AND BAKERY	Whole wheat muffin Taco shell Bran flakes Granola Wheat germ (toasted) Molasses (blackstrap) Rice (brown, whole grain)	Bran muffin Oat flakes (fortified) Peanut butter cookies Custard (baked) Molasses (blackstrap) Rice Pudding
OTHER FOODSTUFFS	Whole milk (dry) Nonfat milk (dry) Eggnog Avocado Fig Peach (dry) Pear (dry) Raisins	Cheddar cheese Edam Gruyère Parmesan Ricotta Sour Cream Whole milk (dry) Yogurt Fig Pear (dry) Papaya

## SUMMARY

There is currently a global Alzheimer's pandemic involving tens of millions of victims. In the USA alone the number of sufferers is expected to reach 14 million by 2050.<sup>42</sup> As the evidence presented in this volume illustrates, this suffering and the associated financial costs are totally unnecessary. Alzheimer's disease is caused by aluminum and is particularly common in those carrying the APO E4 allele(s), who are, in consequence, the most susceptible to this toxic metal.

In my book *Disaster Planning: The Preservation of Life and Property*,<sup>43</sup> published in 1980, I wrote "Communities, like individuals, may often work towards their own destruction through neglect, ignorance, or a deliberate emphasis on fulfilling superficially advantageous short-term goals. Incrementally, in doing so, they magnify risk and eventually suffer the disasters they deserve." It has been known for over a century that aluminum is a neurotoxin. The unfortunate truth that its widespread use, by a calcium and magnesium deficient population, is the major cause of Alzheimer's disease is now unavoidable. Time will tell whether we are intelligent enough to avoid the coming Alzheimer's catastrophe that is now routinely predicted.

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## The Author

The author lives with his wife Sarah and cat McNuff in Victoria, British Columbia. A Canadian by choice, he was born in Tunstall, Yorkshire, England where he was educated at the Hull Grammar School and University College London. While at university, he specialized in geology and geography, earning a B.Sc. in 1964 and Ph.D. in 1968 from London University.

He has been a faculty member in the Department of Geography, University of Victoria since 1967. A tenured professor, he has authored or edited some 230 publications, the majority of which focus on reducing disaster losses or identifying the causes of chronic disease or longevity. He has published hypotheses on the origins of numerous diseases including myocardial infarction, SIDS, cancer, diabetes, schizophrenia, multiple sclerosis, amyotrophic lateral sclerosis, Alzheimer's and Parkinson's diseases, stroke, and AIDS. In May 2004, he was presented with the Orthomolecular Doctor of the Year Award by the International Society for Orthomolecular Medicine.

His many books include *Disaster Planning: The Preservation of Life and Property*, Springer Verlag, New York; *Reducing Cancer Mortality: A Geographical Perspective*, Western Geographical Press, Victoria; and *The Ozymandias Principles*, Southdowne Press, Victoria. Further books by the author include *Health, Disease, and the Environment*, Bellhaven Press (now John Wiley), London, and *What Really Causes AIDS*, Trafford Publishing, Victoria.

He is a member of the Explorers Club and several academic organizations including The New York Academy of Sciences, The Royal Geographical Society, and The Royal Society of Literature. In addition, he is the editor of both the International and Canadian Western Geographical Series and is a member

of the boards of the Journal of Orthomolecular Medicine and the International Schizophrenia Foundation. He has been a consultant to numerous organizations, including the United Nations, NATO, and the governments of Canada, Ontario, and British Columbia.

Every day he takes at least the recommended daily allowance of the known essential nutrients, in the belief that this will slow the aging process. As a consequence, most of his salary is spent in health food stores. His other bad habits include providing treats to all the neighbourhood dogs; losing at chess to his computer; being regularly beaten by his stepson Dan at video games; and, with the assistance of @Derby and various computer models, failing to correctly predict the outcomes of horse races. For a more complete curriculum vitae visit <http://www.hdfoster.com>. A free copy of this book and *What Really Causes AIDS* and *What Really Causes Schizophrenia* can be downloaded at this website.

*The man who discovers a new scientific truth  
has previously had to smash to atoms almost  
everything he had learned, and arrives at the new  
truth with hands blood-stained from the slaughter  
of a thousand platitudes.*

José Ortega y Gasset,  
*The Revolt of the Masses*, 1930



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