A NEW ERA FOR ALZHEIMER’S

IT IS TIME TO START ANEW. More than a century after neuropathologist Alois Alzheimer gave the first scientific talk describing the disease that bears his name today, we have no good treatments for this thief of minds, and we certainly have no cure. Today 40 million to 50 million people worldwide suffer from Alzheimer’s disease and other dementias. The drugs doctors have tried, aimed at a single type of lesion, have repeatedly and agonizingly fallen short. Now scientists are beginning to say it is high time for a fresh approach to the illness.

Patients and their families, of course, have known this for decades. To begin this special section, a husband describes losing his wife to this ailment, and the utter devastation it wreaked on her, on him and on their family (page 28). Then we turn to the spectrum of disease causes, ranging from problems within the brain to the environment outside. Neuroscientists have identified five areas—such as the brain’s immune reactions—that have received relatively little attention yet may hold the seeds of new hope (page 30). We also take a hard look at the “amyloid hypothesis” that has dominated the search for treatments and whether it still holds sway (page 34). Another overlooked area is research into women, who have a much higher risk than men of developing the disease, and our next story chronicles new studies of the roles played by estrogen and menopause in mental decline (page 37). Finally, we examine recent research that shows that air pollution raises the risk of Alzheimer’s to a startling degree and explore the path between dirty air and brain destruction (page 42).

—Josh Fischman
Alzheimer’s took my wife’s memory and her life and tortured our family. There was nothing we—or medicine—could do to stop it

By Joel Shurkin

I have learned that when someone you love has Alzheimer’s, he or she is not the only one facing memory issues. Do we remember the bright, sunny person full of life and creativity, or do we remember the person who no longer recognizes us, who lies in a bed in a nursing home, gasping for air? Do we remember the lover with whom we could share our body, our thoughts and our adventures or the person who cannot finish a sentence or find the bathroom? How do we live with the fact that the individual actually died years before his or her body stopped? The ghastliness of Alzheimer’s seems to push out everything else. I am finding it hard to remember ordinary life with Carol before Alzheimer’s.

My wife, Carol Howard, was diagnosed with early-onset Alzheimer’s in her early 60s. I slowly watched her disintegrate, watched her beautiful mind be deconstructed part by part, watched sentence slowly fade until she was, well, not here.

When she learned the diagnosis, she was determined to fight the disease. She enlisted in two clinical trials of potential drugs, both of which failed. When we realized what was inevitable, she told me that she wanted me to scream for her when she was gone. She was angry that several decades’ worth of Alzheimer’s research had produced no hope. There is no cure; there is no good treatment.

I will tell you who she was and what she became. She was a woman of great beauty, with eyes of summer-sky blue. She was peaceful and brilliant, gentle and kind. I met her when she took a science communication course I taught at the University of California, Santa Cruz. She always put the right word in precisely the right place. Carol studied marine biology and wrote a popular book about her doctoral work with two Atlantic bottlenose dolphins. For 15 idyllic years we lived in the redwood forest of the Santa Cruz Mountains, writing. She eventually moved with me to Baltimore and worked at the Center for Alternatives to Animal Testing at the Johns Hopkins Bloomberg School of Public Health, an excellent job that she loved.

About six years ago odd things began to happen. Carol blacked out occasionally. Her libido disappeared. One night she sat in front of her office computer weeping because she had forgotten how to download a file. She stopped reading books. Soon there was medical testing, and then the dreadful diagnosis.

She still loved walking, but she started getting lost, so I gave her a GPS tracker. When she could not find her way on her own, I would fetch her, or one of our...
neighbors would bring her home. One time she got out of the house (which had not been locked properly) and started shrieking in the street. At a family Thanksgiving gathering she left our bedroom and walked about the house naked. When things got worse, she would sit for hours in a living room chair, staring at nothing, the light in her glorious eyes dead. I would talk to her, tell her about my day, without the slightest reason to think she heard me or would respond. There were two of us in the house, but I was alone.

In January last year I fell, broke my knee and several ribs, and had to be taken to a hospital. Our daughter, Hannah, knowing neither she nor I would be able to take care of her mother, found a good nursing home for Carol that took Medicaid. I recovered and regularly visited her twice a week, monitoring her decline. She once thought I was her father. On two occasions I saw her physically resist help, showing a fierce aggression I never thought possible in her.

The end is an image that will not go away. At noon on October 25, 2019, with Hannah and a friend holding her hands, Carol raised her body slightly, made a gurgling sound and fell back, dead. I closed her eyes. It was a month before her 70th birthday and a month before our 28th anniversary.

One result was financial disaster—the only possible end for many Americans in our dysfunctional health care system. We had to hire lawyers to handle the legal issues ($12,000). I was told that to pay for Carol’s nursing home, which cost about $80,000 a year, I had to impoverish myself to qualify for Maryland Medicaid: our attorneys said that I could have no more than $2,500 in the bank. We had to spend Carol’s retirement funds, and I had to give up our house and move into an apartment. My life now is upside-down.

So how do I remember her? Her decline and death are more recent, so they are naturally stronger memories. But how do I deal with the horror and indignity of Alzheimer’s? The eyes whose light had dimmed? The soiled diapers? The unfinished sentences? The empty bank account? The anger?

I should remember this: Three and a half years ago, before Carol’s decline became precipitous, I found out that the Royal Concertgebouw Orchestra, one of the world’s best, was playing my favorite piece of music—Gustav Mahler’s Resurrection Symphony—in Amsterdam. Carol agreed that we had to go.

The concert was stunning. Afterward we walked, holding hands, across a grassy park in a light mist that muted the great city. Carol said not a word. I could tell from her face that she was present and aware and, better yet, that whatever Mahler was saying in his passionate music, she had understood. He had gotten through to her. Scientists say music appreciation is one of the last things to go with Alzheimer’s because of where it is processed in the brain.

It was the last time we made love and the last time I had Carol back for any length of time—the living, wise, beautiful Carol. The Carol of the summer-blue eyes. I keep reminding myself.
Our inability to come up with a good treatment for Alzheimer’s means it is time to reexamine the basic biology of the disease. Progress in five fundamental areas may lead to fresh hope

By Kenneth S. Kosik

No fundamental obstacle prevents us from developing an effective treatment for Alzheimer’s disease. Other troubles of human nature, such as violence, greed and intolerance, have a bewildering variety of daunting causes and uncertainties. But Alzheimer’s, at its core, is a problem of cell biology whose solution should be well within our reach. There is a fairly good chance that the scientific community might already have an unrecognized treatment stored away in a laboratory freezer among numerous vials of chemicals. And major insights may now reside, waiting to be noticed, in big databases or registries of clinical records, neuropsychological profiles, brain-imaging studies, biological markers in blood and spinal fluid, genomes, protein analyses, neuron recordings, or animal and cell culture models.

But we have missed those clues because for decades we have spent too much time chasing every glossy new finding in Alzheimer’s research and too little time thinking deeply about the underlying biology of this ailment. Instead our work has been driven by a number of assumptions. Among those assumptions has been the central and dominant role of the protein fragment called beta-amyloid. A large amount of data supports the idea that beta-amyloid plays an important part in the disease. We have developed drugs that can reduce concentrations of the protein fragments in people with Alzheimer’s, yet by and large they have not stopped patients’ cognitive decline in any meaningful way.

It now seems simplistic to conclude that eliminating or inhibiting beta-amyloid will cure or treat those suffering from the disease, especially without far deeper and more comprehensive knowledge of how it develops and progresses [see “The Amyloid Drug Struggle,” on page 34]. We have not been barking up a completely wrong research tree, but our zeal has led us to ignore other trees and even the roots of this particular one.

It is time to go back to basics. I have been a scientist involved in Alzheimer’s research for three decades, part of large projects investigating families with a high risk of Alzheimer’s, prevention strategies
and the physiology of damage to brain cells that is part of the illness. I and my colleagues, who work across many scientific and medical disciplines, believe that we need to reexamine the fundamental physiology and biology of Alzheimer’s, as well as reassess the contents of databases and our lab refrigerators for clues that we may have overlooked. This approach will let us develop theories and models of the way this illness progresses, and we can use those ideas to derive novel strategies to combat the disease.

There are at least five potentially fruitful and timely research directions—areas based on important discoveries made in the past several years—that can extend our knowledge, and I believe that they are quite likely to yield insights needed to find effective treatments. These areas range from malfunctions in the way brain cells get rid of problem proteins, to damage caused by inflammation, to trouble with the ways that cells send electrical signals to one another. These are different domains, but in a person they overlap to create illness in the brain, and individually or in tandem they may lie behind the terrible damage done by Alzheimer’s.

**PROTEIN-DISPOSAL PROBLEMS**

Beginning in the early 1990s, several neuropathologists—including Alois Alzheimer, the scientist after whom the disease is named—described microscopic lesions in the brains of patients who had died with various forms of dementia. Today we know these are clumps of misshapen proteins. In the case of Alzheimer’s, some of the clumps consist of pieces of beta-amyloid protein. They sit between neurons and are called senile plaques. Other clumps reside within neurons, made of a protein known as tau, and are called neurofibrillary tangles.

What we still do not know, more than a century later, is why cells fail to remove these abnormal lumps. Cellular mechanisms for the removal of damaged proteins are as ancient as life itself. What has gone wrong in the case of Alzheimer’s? This question is as central to the disease process as a loss of control over cell proliferation is to the progression of cancer. Some recent observations from researchers at the Washington University at St. Louis, among other institutions, indicate that abnormal proteins may find their way out of cells, perhaps evading their natural detection systems for bad molecules. We do not know how they do so, but figuring it out might be a very useful way to start a new search for how and why Alzheimer’s progresses.

Cells have two major systems for the removal of abnormal proteins: the ubiquitin-proteasome system (UPS) and autophagy. In the former, proteins are inserted into a barrel-shaped cell structure called the proteasome, where they are chewed up into reusable parts; in the latter, the cell wraps up aberrant proteins and totally destroys them. In neurons, these systems are co-opted to control the composition of cell-signaling connections—formed by anatomical structures known as axons, dendrites and synapses—as they are strengthened or weakened during learning. (Sometimes neurons extrude damaged proteins and turn over their destruction to microglia, brain cells that are part of the immune system.)

The decision about whether to shuttle an abnormal protein toward the UPS or autophagy is mainly based on the protein’s size. The proteasome has a narrow, pore-like opening at each end that can accept a small, fine, threadlike protein strand. Inside it are enzymes that break the protein down into its constituent amino acids, which are recycled for use in the synthesis of new proteins. Larger molecules that do not fit into the proteasome, such as protein clumps and old, misshapen proteins with age-related damage, get shuttled toward the autophagy system and its more powerful engine of destruction, the lysosome.

In Alzheimer’s, something goes wrong and leaves brain cells with these chunks of tau and amyloid that further damage or choke them. So we could learn an enormous amount about the pathology of Alzheimer’s if we understood the details of these systems. We need to examine specific differences in the degradation pathways in different subtypes of neurons, as well as the precise mechanism by which these disposal systems recognize abnormal proteins. Malformations in proteins such as tau do not happen in a single step. Proteins may harbor mutations and accumulate modifications that predispose them to misfolding, which can be followed by aggregation into larger and larger structures in a multistage process. As proteins progress along this pathway, at what point do surveillance systems kick in and recognize them as abnormal? In-depth knowledge about these kinds of processes could lead us to a more strategic approach to treatment and intervention with drugs.

One intriguing finding that plays into...
our understanding of such evasion is that tau can travel out of cells and into the spaces between them, and from there it gets taken up by neighboring cells. What purpose this transit system serves is unknown. Is exchange of the protein among cells normal, or do cells disgorge abnormal tau to rid themselves of a toxic substance? We think that in Alzheimer’s, at least some of the tau protein outside cells is already misfolded. We believe this because when such tau enters a neighboring cell, it forms a template, an abnormal pattern, that other tau proteins in that cell use to shape themselves in similar odd ways. When it spreads, tau in neighboring cells copies the specific shape of the entering tau protein.

The observations of tau outside cells have prompted some to speculate that the protein could be intercepted and cleared at that point by an antibody delivered to the patient. But that approach is unlikely to work unless we know exactly how tau is misshapen when it does its damage. This precise structure is necessary information for designing a highly specific antibody. Another open question is where tau resides in the complex space between cells. More specifically, does it move across synapses, where two neurons transmit their signals? This synaptic cleft is a narrow gap that is not easily accessible to an antibody. Potentially more promising approaches are to understand exactly how tau is extruded from cells and the receptors that neighboring cells use to pick the protein up; recent experiments in my lab may point to the identity of one such receptor.

**IDENTIFYING PROTEIN CHANGES**

One major recent advance in Alzheimer’s research was the imaging of abnormal tau within a cell, snarled in a neurofibrillary tangle, at a level of detail never before seen. This remarkable image, published in 2017 in *Nature*, showed thousands of tau proteins aligned as pairs tightly locked in a C-shape configuration. It is possible that features seen in this solid inclusion could provide the information necessary to design small molecules that fit within the crevices of the abnormal protein and pull it apart to disrupt the disease process.

But breaking up these structures is a challenging goal for many reasons, not the least of which is how strongly the whole tangle is held together. A more successful direction could be to determine the sequence of microscopic events that takes these tau proteins from their typical liquidlike state to the more rigid and solid state seen in that image and to discover the protein modifications that predispose tau toward this change.

The switch from liquid to solid is called a phase transition. Biologists’ interest in such transitions in living cells is now surging because of their possible role in disease. Physical chemists have studied phase separation, such as the condensation of oil drops in water, for many years. Oil and water are both liquids, yet they remain separated because of a balance of attractive and repellent forces. The advantage of phase separation for living cells is that it concentrates a specific set of molecules in one place, which aids certain cellular activities. Multiple proteins near a gene, for instance, can condense to control the expression of that gene, as shown in a 2018 paper in *Science*. Such a condensed set of proteins, though still in a liquid state, do not diffuse away; they are held together as a droplet by weak physical forces. This configuration allows sets of proteins to move and work together without being wrapped together in a membrane, which would require resource-costly maintenance from the cell.

Some proteins, such as tau, are tightly packed when they are located within a droplet, and the high concentrations could make them prone to aggregation into a tangle. Proteins that form droplets in this way share a property known as intrinsic disorder. Like the Greek god Proteus, they can assume numerous shapes, in contrast to more ordered proteins that are limited to a few specific forms. Different shapes require different energy levels. At times, some intrinsically disordered proteins fold into such a low energy state that they cannot shift out of it, which essentially increases their rigidity. And that may exacerbate their tendency to tangle together.

Cells also pack proteins and other mol-

---

**Cleaning Out Bad Proteins**

The two classic hallmarks of Alzheimer’s are clumps of a protein fragment called beta-amyloid and tangles of a protein called tau. Brain cells’ systems for getting rid of abnormal proteins fail in this illness, and scientists would like to understand what goes wrong. Normally cells use two elimination methods. Smaller single proteins are shuttled to the ubiquitin-proteasome system, which involves a barrel-shaped organelle (the proteasome) that chops the proteins into amino acids. Larger clumps, or aggregates, are handled by autophagy, in which clumps are encapsulated so they can be broken down by enzymes from another organelle, the lysosome.
THE AMYLOID DRUG STRUGGLE

A leading idea for Alzheimer’s treatment is getting a harder—and sometimes more skeptical—look

By Tanya Lewis

In March 2019 biotechnology giant Biogen stopped two big trials of its experimental Alzheimer’s disease drug aducanumab because it did not appear to improve memory in declining patients. Then, in a surprise reversal several months later, the company and its partner, Japanese drugmaker Eisai, said they would ask the U.S. Food and Drug Administration to approve the treatment. A new analysis, Biogen said, showed that a subset of people on the highest doses in one trial did benefit from the compound, which dissolves clumps of a protein called beta-amyloid within the brain.

The back-and-forth decisions, along with the failure of a slew of other amyloid-clearing compounds, have left experts divided about whether treating amyloid buildup—long thought to be the best target for an Alzheimer’s therapy—is still a promising approach.

Some of the scientists rethinking the so-called amyloid hypothesis helped to generate it in the first place. “I would say it has legs, but it’s limping,” says geneticist John Hardy, who co-authored the genetic studies that pioneered the idea more than two decades ago. According to Hardy, who runs a molecular neuroscience program at University College London’s Institute of Neurology, “the [concept] we drew in 1998 is cartoonishly oversimplified. There were lots of question marks. We thought those questions would be filled in within a couple of years. And yet 20 years later they are not filled in.” Other experts, though, still contend that the amyloid hypothesis is a strong explanation and that treatments targeting the protein are the right way to go.

Beta-amyloid forms when amyloid precursor protein (APP) is chopped up by the enzymes beta-secretase and gamma-secretase. The beta-amyloid fragments are normally broken down further. But in people with Alzheimer’s, beta-amyloid accumulates around neurons. In addition, tangles of another protein, tau, form within neurons. These changes are ultimately followed by cell death and brain degeneration, which prompted suspicions that beta-amyloid was a cause. And people with a particular genetic form of Alzheimer’s have mutations in one of three genes that code for APP and two components of gamma-secretase called presenilins. Their brain cells have trouble getting rid of beta-amyloid. Further evidence about amyloid came from individuals with Down syndrome, who have an extra copy of chromosome 21—which carries the gene for APP—and thus make more of the protein. These individuals also have a high risk of developing dementia by age 50. Such discoveries led scientists to infer that a faulty amyloid-clearing mechanism was to blame in the disease.

But the numerous drug failures have led some to reconsider the effectiveness of aiming therapies solely at amyloid. Beta-amyloid often accumulates for years before symptoms start, and not everyone who has this pathology goes on to develop the disease. In February two amyloid-targeting drugs, Eli Lilly’s solanezumab and Roche’s gantenerumab, failed in a clinical trial for an early-onset, genetic form of the disease thought to be directly tied to amyloid metabolism.

A convergence of research, including work from the Alzheimer’s Disease Cooperative Study, supported by the U.S. National Institute on Aging, suggests that amyloid buildup is just one part of a complex cascade of interactions. “Our experiences with a variety of interventions targeting amyloid clearly have brought us to [this] point,” says Howard Feldman, director of the cooperative study, which is a consortium of academic and government laboratories that conducts clinical trials of Alzheimer’s treatments. “It seems very difficult that a single amyloid intervention is going to stem the tide of the disease.” Although the hypothesis may be a good explanation for the early-onset, genetically driven forms of the disease, the late-onset form probably involves multiple problems, so approaches aimed only at amyloid are unlikely to work, says Feldman, who is also a professor and clinical neurologist at the University of California, San Diego.

Some researchers, such as Karen Duff of Columbia University, favor the idea that tau protein tangles play a part that is as big as or bigger than that of beta-amyloid. One reason is that the degree of tau pathology more closely correlates with the seriousness of cognitive symptoms than amyloid pathology does.

Other scientists think inflammation or defects in the blood-brain barrier may play a critical role. But drugs targeting tau and inflammation have so far been ineffective,
Feldman notes. He believes that a combination of interventions might be the best approach: “A single intervention may never be sufficient, outside of genetic [early-onset] forms of disease.”

There are other ideas as well. In recent years Hardy and his colleagues have come to view late-onset Alzheimer’s and other neurodegenerative diseases as the result of a faulty response. They believe that the early accumulation of beta-amyloid might damage neuronal cell membranes, and if immune cells called microglia fail to remove these damaged membrane proteins, it could prevent the cell membranes from adequately clearing more amyloid—spurring a cycle of damage. Recent genome-sequencing studies support this idea, Hardy says: the majority of genes identified as risk factors in late-onset Alzheimer’s involve microglial metabolism; others encode proteins that help to build and repair cell membranes.

Some scientists still believe that amyloid has a primary role because of several studies linking its aggregation to the seriousness of symptoms. “In my view, the hypothesis is very much alive and well,” says David Holtzman, chair of neurology at the Washington University School of Medicine in St. Louis. “There’s no question that science says beta-amyloid is important in the disease. The question is, When can it serve as a treatment?”

Hardy, though more skeptical than he was decades ago, thinks that the hypothesis has strong data behind it, and he believes that amyloid drugs might yield poor results because they are given far too late in the disease’s progression. “If I was having a heart attack, a statin might be the right drug, but it’s too late,” he says. Clinicians may eventually be able to measure genetic, blood or spinal fluid biomarkers to predict who is at risk of developing Alzheimer’s, which would make it possible to treat them before they develop symptoms.

Others say amyloid’s real importance might be as one of those biomarkers. “I think amyloid is a critically important marker to understand risk and how early we can diagnose,” says Denise Park, chair in behavioral and brain sciences at the University of Texas at Dallas, who studies brain aging. “I don’t think there’s anything right now that is better.”

Going forward, it seems unlikely that the field will abandon the amyloid hypothesis. But scientists do seem, after a long time, poised to take a broader view of other processes at work in this destroyer of minds and memories.

Tanya Lewis is an associate editor covering health and medicine at Scientific American.

ecules prone to phase transitions in membraneless organelles called stress granules and RNA granules. When certain proteins and RNAs coalesce in such granules, they pack tightly together but typically remain in a liquid state. At a certain density, however, they may become predisposed to more clumping and to a phase change to a solid, a change that would increase their ability to cause brain damage and would make them harder for cell-disposal systems to remove. That is why we need to better understand the conditions that trigger this process.

THE INFLUENCE OF GENES

In middle-aged people, Alzheimer’s can arise from genetic mutations in three genes (APP, PSEN1 and PSEN2) that cause a rare familial form of the disease, a frightful inheritance passed from one generation to the next. But the vast majority of the time, Alzheimer’s shows up in individuals older than 65 and does not involve these genes. By combing through tens of thousands of genomes, geneticists have now discovered other DNA changes, about two dozen gene variants, that do increase risk by a small amount. The most influential of these alternative forms is a version of the gene APOE known as the ε4 variant. A combination of several risk-gene variants adds to one’s likelihood of getting the disease. (Because gene variants are frequently associated with ethnicity, we need a much more inclusive data set than the mostly Caucasian-based gene analyses and registries currently available to make a reliable assessment of genetic risk in all populations.)

Each of these variants opens a different door through which we can explore the ways that a small change in our genome can heighten our likelihood of acquiring Alzheimer’s. Some of the more frequently seen variants, and thus the most interesting doors, are genes or other stretches of DNA in the microglia. In a 2019 Science paper examining these immune system cells, scientists found one variant associated with Alzheimer’s risk in a gene known as BIN1. This gene is normally involved in the way microglia engulf potentially harmful outside molecules and move them into the cell, protecting nearby neurons. The variant can affect how efficiently microglia clean up stray proteins.

In microglia and other cells, certain gene variants are also associated with age and sex. Differences exist between men and women, for example, for genes on the 22 pairs of non-sex chromosomes and for genes expressed on the X and Y chromosomes. The effects of these variants may have something to do with the higher rates of Alzheimer’s in women, which hold even with correction for women’s longer life spans [see “The Menopause Connection,” on page 37]. Overall the small effects of any single gene variant associated with Alzheimer’s probably contribute, each in its own limited way, to individual differences in the way we handle amyloid and tau accumulations. We need to nail down the how and why of these contributions.

TAMING INFLAMMATION

When the brain detects a source of damage such as amyloid plaques or tau neurofibrillary tangles, it sounds an alert and releases a barrage of immune system molecules called cytokines, along with a variety of attack cells. This response stems from the microglia, in large part, and it causes an inflammatory reaction intended to destroy any tissue harboring the trouble spots. This brutulike “innate” system operates quite differently from the more refined “adaptive” immune system, which generates immune cells and antibodies that react only to specific invaders, such as bacteria or viruses, and that mount a narrower, more precise defense. The broader innate response dominates in Alzheimer’s. As the lesions proliferate beyond the ability of a neuron’s internal machinery to get rid of detritus, this general inflammatory response kicks in and, unfortunately, often hits still healthy cells in the brain. Scientists at the University of California, Irvine, recently have found that eliminating the aged microglia in older mice prompted the animals to repopulate their brains with fresh microglia. This rejuvenation improved spatial memory, reversed age-related changes in neuronal gene expression, and increased the birth of new neurons, as well as the density of their dendrites.

This assault triggered by amyloid and tau probably happens on top of a low level of inflammation in the brain that occurs naturally with aging. Many older people have increased concentrations of pro-inflammatory cytokines such as tumor necrosis factor (TNF), suggesting that a slight inflammatory state exists throughout the body at this point in life. Aging is highly
variable among humans, and the differences mean the progress and the effects of Alzheimer's are quite variable as well. Some of this diversity can probably be attributed to individual variation in human immune systems. Different people inherit distinct configurations of genes involved in immune responses. In addition, during our lives our systems are shaped by non-heritable influences. We get different exposures to symbiotic microbes in places such as our gut and to pathogenic microbes from our surroundings. This all suggests that exposure of the immune system to various pathogens, as well as our genetic differences, may contribute to the way Alzheimer's develops by establishing an individual immune profile, or "immunotype."

The challenge for researchers who want to stop the brain damage caused by widespread inflammation is to distinguish the desirable immune responses the brain uses to combat developing problems and ordinary age-induced degradation from the other, more reckless immune responses to the advancing pathology of Alzheimer's. The research community would like to tame brain inflammation caused by the disease but does not yet know how to deliver an intervention with precision.

**ELECTRICAL DISCONNECTIONS**

The brain is an electrical organ. Its most defining feature is its ability to encode and convey information in the form of electrical signals passed between neurons, usually by chemicals called neurotransmitters. How Alzheimer's impairs brain cells' signaling and disrupts the way they assemble into functional memory circuits has been insufficiently studied. But now the ability to detect both structural and functional connections is burgeoning thanks to technical advances that allow us to visualize these links in exquisite detail.

Some of these advances involve optogenetics, a way for scientists to stimulate specific neurons in an animal's brain using light. Researchers can offer the animal a reward or fearful experience, then detect which genes become more active. This approach, in an impressive achievement, is now allowing researchers to observe and manipulate specific neurons that encode a specific memory known as an engrun, as noted in a 2020 paper in *Science*. When those cells were stimulated by light alone after the initial experience, the memory of it was recalled. If we can figure out the biology that drives the formation of these electrical memory connections, that information will be crucial in helping us understand how Alzheimer's pathology interrupts this neural circuitry.

Neuroscientists made another advance this year when they discovered that microglia seem to be involved in making the brain forget these engrams by eliminating the synapses that normally connect neurons.

We also know that neurotransmitters are affected in different ways by some of the proteins involved in Alzheimer's pathology. Tau, for instance, accumulates in neurons that use the neurotransmitter glutamate and work to excite signals. But other neurons that inhibit signals—signaling relies on good start-and-stop mechanisms—release a different neurotransmitter, GABA, and are less affected by tau accumulation. The basis for this cellular selectivity and its consequences is unknown, and we need to understand it much better. Scientists have also seen that neuronal activity enhances tau's spread, which could be another important part of the Alzheimer's puzzle.

Not only are signaling cell types affected differently by the disease process, but effects vary in different brain areas, too. For example, areas of the brain related to memory, emotions and sleep are severely damaged, whereas centers related to primary motor and sensory function are relatively spared. One study found that regions of the brain activated when our minds wander, the so-called default or resting state, are the same places where amyloid plaques are first deposited. But we must be cautious in drawing conclusions—a wandering mind does not necessarily cause amyloid deposition.

Sleep is another electrical state of the brain that is increasingly recognized as a factor in the development of Alzheimer's. Levels of both amyloid and tau fluctuate during the normal sleep-wake cycle, and sleep deprivation acutely increases the production of amyloid and decreases its clearance. Deep sleep evokes rhythmic waves of cerebrospinal fluid that may serve to clear toxins, including amyloid, from the brain. Unfortunately, this kind of sleep diminishes with aging. This observation could stimulate work on pharmacological approaches designed to specifically restore deep sleep.

**SHARED IDEAS**

These research areas are not the be-all and end-all of a rejuvenated Alzheimer's science agenda. There are certainly more. But these five avenues are intertwined and, like biology itself, can be investigated in many cross-fertilizing ways. One hope I have is that basic science fills in missing information—particularly quantitative information—computational modelers and theoreticians will step in to help predict the impact of Alzheimer's pathology on brain circuitry and cellular pathways. I also would like to see these research directions prompt investigators to think collectively and systematically and to share their ideas in constructive ways. This is how we can come together to push back our ignorance about this terrible disease.
THE MENOPAUSE CONNECTION

Getting older is the biggest risk factor for Alzheimer’s. Research indicates that being female is a close second. Why?

By Jena Pincott

This is how memory loss begins, Sophie tells me: You show up at work, forgetting that you are supposed to be at a breakfast meeting with a client. You blank on the names of your neighbors. Soon enough you walk into a room without any clue as to why you are there. Sophie, a lawyer in her early 50s, who asked to go by a pseudonym, had been suffering from frequent hot flashes and night sweats, both associated with menopause, but the forgetfulness seemed to be in another league. What was happening to her mind?

Lisa Mosconi, director of the Women’s Brain Initiative and associate director of the Alzheimer’s Prevention Center at Weill Cornell Medical College in New York City, might know. She has analyzed thousands of positron-emission tomography (PET) scans of patients entering menopause and has seen how their brain metabolism changes over time. “In premenopause, your brain energy is high,” Mosconi says, showing me a PET scan of a young woman’s brain. It is lit up by many bright red and orange blotches representing high glucose metabolism—a proxy for neuronal activity. In perimenopause, which hits women in their mid- to late 40s, brain glucose metabolism slows by 10 to 15 percent or more, and the scan changes: red and orange spots give way to more yellows and greens, representing less sugar uptake and lower metabolism. “Then, in postmenopause, brain glucose metabolism slows down 20 to 30 percent, sometimes more,” Mosconi says, showing me the final scan. Now, clearly, the greens have gained territory.

Estrogen is the master regulator of metabolism in the youthful female brain, orchestrating everything from glucose transport and uptake to its breakdown for energy. Mosconi’s scans are rainbow-colored evidence that decreased levels of the hormone during menopause, which often starts when women are between the ages of 45 and 55, lead to a “bioenergetic brain crisis,” as she describes it. At some point during this seven-plus-year transition period, up to 60 percent of women experience what is known as menopause-related cognitive impairment: bouts of confusion, distractibility and forgetfulness. These memory problems are normal. The generation of synapses requires energy; as estrogen levels and brain glucose metabolism decline, so does the formation of new connections between neurons. Fortunately, the impairment is temporary: women rebound, their wits intact, as the brain compensates and taps other sources of energy. A 2009 study found that newly postmenopausal women...
score just as well on cognitive tests as they did before the transition. Decades later, however, roughly a fifth of them will be diagnosed with Alzheimer’s disease. Mosconi and others believe that for many of the 3.6 million women living with the disease in the U.S. alone, menopause might have been a tipping point for cognitive decline.

Although investigations of Alzheimer’s that focus on women have become a top priority, too many questions remain unanswered when it comes to female-specific risk factors, symptoms, prevention and responses to treatments for the disease. Why in the U.S. does a woman have a one-in-five lifetime chance of developing the disease at age 65, compared with one in nine for a man at the same age? American women live an average of five years longer than men, but “longevity does not wholly explain the higher frequency and lifetime risk,” noted an expert panel representing the Society for Women’s Health Research in a 2018 analysis. Why are females who carry the e4 variant of the gene APOE (APOE4), which increases the risk of Alzheimer’s, likely to acquire the disease at a younger age than male carriers? What is it about women’s biology and life experiences that makes them more vulnerable?

The menopause hypothesis—that decline in estrogen levels in this period renders the brain vulnerable to future damage—could offer answers. If Mosconi and other researchers are right, Sophie and the millions of women worldwide who pass through this transition could benefit from lifestyle interventions and, conceivably but controversially, hormone therapy (HT) to prevent the disease.

THINKING WITH LESS ESTROGEN

“It’s starvation mode,” says Roberta Diaz Brinton, director of the Center for Innovation in Brain Science at the University of Arizona, describing what happens when estrogen declines and green patches take over in menopausal women’s PET scans. Estrogen plays multiple and wide-ranging roles in brain bioenergetics, she explains. A signaling molecule with receptors throughout the brain, it regulates mitochondria, which generate energy for cells and fuel the formation of neuronal connections. Estrogen also activates the enzymes that enable synapses to function, and it facilitates glucose transport from blood vessels into the brain and from the brain into neurons and glia, the cells that support and protect neurons. Brinton’s research on aging female mice has shown that as estrogen levels fall and glucose metabolism slows down, the brain adapts by using ketone bodies—substances produced from fatty acids, in this case from white matter, including the myelin sheaths that protect neurons—as a supplemental fuel source. This switch—essentially an act of self-cannibalization—also appears to occur to some degree in women, and those whose brains draw more heavily on ketone bodies may suffer greater degeneration of white matter and a higher risk of dementia.

Sometimes a brain energy deficit coincides with the development of hard deposits, or plaques, of beta-amyloid protein. They can show up in some brains that function normally, but every person with Alzheimer’s has them. They are thought to interfere with synaptic signaling. In brains of those with the disease, beta-amyloid usually comes along with tau, a tangled protein that wraps around the nucleus inside cells, apparently killing them by blocking nutrient transport. Moreover, low estrogen increases the permeability of the blood-brain barrier, potentially exposing the brain to toxins or infections that can stimulate an aggressive immune response, releasing proteins that seed new plaques and tangles.

In contrast to the brains of women in their 40s and 50s, Mosconi says, brains of males in the same age group are not found to have aged significantly, and fewer have beta-amyloid plaques. One explanation is that testosterone, like estrogen, is neuroprotective—and levels of testosterone never drop as steeply or abruptly in andropause as estrogen’s do in menopause. This difference might help explain why fewer men get the disease. Alzheimer’s pathology may also develop earlier in women than in men, Mosconi explains, but they compensate so well that they are often not diagnosed until the disease has progressed to a later stage. A 2019 study found that women whose PET scans show biomarkers of Alzheimer’s outperform their male counterparts on verbal memory tests. If cutoff scores were sex-specific, the disease could be caught earlier, when intervention is more effective.

To further identify women at risk, researchers have begun to investigate connections between Alzheimer’s and lifetime exposure to estrogen. Scientists measure estrogen exposure in terms of the “reproductive period”—the time span between a woman’s first menstrual period and her last. A large-scale study of 15,754 members of the health care consortium Kaiser Permanente found that women with a 21- to 34-year reproductive period have a 26 percent higher chance of developing dementia than those with a 39- to 44-year period, suggesting that late onset of menstruation or early menopause poses a higher risk. Yet many factors affect women’s lifelong estrogen exposure, and their impact is understudied. For instance, a woman’s circulating estrogen is dramatically elevated during pregnancy, but after she gives birth it drops and, for several years, remains at a lower level than that in women who have never been pregnant. But studies that sought to link the number of times a woman has given birth to Alzheimer’s risk yielded conflicting results. More than 100 million women worldwide take birth-control pills, which suppress ovarian hormones, yet shockingly little is known about their long-term effects on dementia risk.

THE HORMONE THERAPY DILEMMA

Sophie, who started taking the pill when she reached puberty and who has never given birth, says her memory loss peaked in her last year of perimenopause. She often experienced more than three hot flashes an hour—a frequency and severity that correlate with increased deregulation of glucose metabolism in the brain, greater loss of white matter and a potentially elevated risk of dementia later in life. Sophie’s doctor prescribed a new pill: a combination estrogen-progesterin tablet (progesterin protects the uterus). The effect, Sophie says, was “eerily miraculous”: her hot flashes faded, and suddenly she was remembering breakfast meetings again.

It might seem that every menopausal woman should undergo hormone therapy for brain health alone, but the reality is more nuanced. In the early 2000s the National Heart, Lung, and Blood Institute reported results from its massive Women’s Health Initiative study and its ancillary memory study showing that HT, usually estrogen plus a progestin, is linked with a heightened risk of breast cancer, stroke, heart disease and blood clots and—in shocking defiance of all expectations—a twofold-higher rate of dementia. Investigators have since identified flaws in the study. Women were prescribed conjugated equine estrogen, a semisynthetic form thought to be less neuroprotective than the 17β-estradiol commonly used today. But a bigger problem was that the women were 65 or older when they started HT.

A woman’s age when she takes her first HT pill (or applies her first cream, ring or patch) is central to what Brinton calls the
The Burden of Alzheimer’s

Deaths
In the U.S., Alzheimer’s disease is the sixth leading cause of death, and experts note it may be underreported because death certificates often list the immediate cause, such as pneumonia, and not the underlying dementia.

10 Leading Causes of Death in the U.S., 2017 (age-adjusted death rates)

- Heart disease
- Cancer
- Unintentional injuries
- Chronic lower respiratory disease
- Stroke
- Alzheimer’s disease
- Diabetes
- Influenza and pneumonia
- Suicide
- Kidney disease

Deaths per 100,000 people

Gender Differences
Women in the U.S. suffer from Alzheimer’s at a higher rate than men do, according to estimates from the Institute for Health Metrics and Evaluation. Beginning at age 50 and continuing through age 95, there are more and more women among newly diagnosed cases. A similar growing gap between women and men emerges when the disease is measured by the number of years—based on average life span—lost to disability or early death from the illness.

A WINDOW OF VULNERABILITY

Menopause does not cause Alzheimer’s. It is more a window of vulnerability—especially for women with underlying risks, Brinton says. At first glance, its connection with Alzheimer’s is not obvious. The average age of women at menopause is 51; the average age for a diagnosis of Alzheimer’s is 70 to 75. That is a 20-something-year gap. But the so-called prodromal phase—between initial pathology such as beta-amyloid plaques and full-blown cognitive impairment—is also about 20 years. “Maybe the timing is a coincidence,” Brinton observes. “But I don’t think so.”

Brain scans aside, is it possible to predict a woman’s Alzheimer’s risk earlier on, when she is still healthy? In a study published in 2016, Brinton and her colleagues sorted 500 healthy postmenopausal women into three groups: metabolically optimal, borderline high blood pressure and borderline metabolic health. Only one group scored significantly lower on verbal memory tests: women with borderline-unhealthy metabolic health.

Technically, these subjects’ metabolic measures were still in the normal range. Yet there were clues that their health was going in the wrong direction. For one, blood glucose levels in this group were nearing the threshold of prediabetes, a condition that afflicts about 30 percent of women and is itself linked with cognitive impairment. After a meal the hormone insulin helps glucose enter cells for use as energy, but in someone with prediabetes, cells in the body start to resist insulin. When brain cells become resis-
tant to insulin, they absorb glucose but fail to respond to it—which, compounded by the menopausal slowdown in glucose metabolism, can contribute to neurodegeneration. For many women in this transitional phase, prediabetes is a prelude to type 2 diabetes, which almost doubles Alzheimer’s risk. More than 80 percent of Alzheimer’s patients are insulin-resistant.

Once we think of menopause—and estrogen depletion—as changing the ecology of the entire body, it is easy to see how a complex array of factors might give rise to Alzheimer’s and why managing those factors is key to prevention. Estrogen’s healthy effects on the cardiovascular system include cholesterol regulation: it raises levels of “good” HDL (high-density lipoprotein) cholesterol and decreases those of the “bad” LDL (low-density lipoprotein) type that causes the buildup of fatty, waxy deposits in arteries. The APOE gene mediates the metabolism of cholesterol and transports it to neurons; carriers of the e4 gene variant have naturally higher levels of LDL cholesterol in the bloodstream and accompanying hardening of the arteries. Loosened by inflammation, these deposits cause “silent strokes” that more than double the risk of Alzheimer’s and other forms of dementia.

Sleep also plays a key role in regulating metabolism, including insulin sensitivity, and deficient sleep affects women disproportionately, especially during menopause. During a normal night of rest, glial cells flush out beta-amyloid and tau proteins. Sleep deprivation disrupts this process, causing the proteins to build up and form plaques, which lead to fragmented sleep, which impairs glucose metabolism, which also interferes with sleep, and so on in perilous loops that accelerate neurodegenerative processes. Again, APOE4 status increases the risk: carriers have a reduced capacity to clear or degrade plaques and tangles.

Stress, too, can move the tipping point during menopause. A 35-year longitudinal study found that the more stressors lasting a month or more women experienced in their 40s and 50s, the likelier they were to have Alzheimer’s four decades later. Along with stress, women are more likely than men to report depression, which is associated with a nearly doubled dementia risk. Unsurprisingly, female APOE4 carriers, who, again, have the strongest genetic risk of Alzheimer’s, are four times more susceptible than noncarriers to clinical depression, possibly because of increased numbers of beta-amyloid plaques in brain regions involved in emotion regulation.

A WINDOW OF OPPORTUNITY

In 2019 Brinton and her colleagues published a follow-up to their study of metabolic indicators, this time with APOE status as a new variable. People with a single copy of the APOE4 gene, which is present in about 25 percent of the overall U.S. population, are more likely to acquire Alzheimer’s than others are and represent about 40 percent of all cases. Women develop the disease much earlier than male carriers, between the ages of 65 and 75, possibly because of the loss of estrogen’s neuroprotective effects. Carriers have higher LDL cholesterol, more beta-amyloid plaques and tau tangles, reduced hippocampal volume and greater decreases in brain connectivity compared with noncarriers. During the menopausal drop in brain glucose metabolism, female carriers of the e4 allele may rely more on the brain’s ketone bodies as an auxiliary fuel.

As in Brinton’s previous study, the group at risk for poor metabolic health had lower scores on some cognitive tests. But this time the analysis revealed that APOE4 carriers were the main drivers of the group’s poor performance. Among carriers, high cholesterol and other effects of poor metabolic health exacerbated the negative effects of APOE4, leading to early cognitive decline. When carriers in the poorly performing group underwent HT, however, their metabolic health improved, along with their scores on some cognitive tests.

But Brinton sees APOE4 status as “a wake-up call, not a death sentence”: plenty of women with APOE4 do not have the disease. In her study, the group with optimal metabolic health, which had the best scores on cognitive tests, included carriers of the Alzheimer’s gene. Were those women, along with healthy noncarriers, better at compensating for the “bioenergetic crisis” of menopause? Did their fitness offset other risk factors?

At least one third of Alzheimer’s cases are linked with diabetes, obesity, poor diet, and other factors that are preventable and treatable, according to an oft-cited 2017 report in the Lancet. “The take-home message is that sustaining metabolic health sustains cognitive health,” Brinton concludes. “You can’t change your chromosomal sex or age or your gene variant. But you can change your metabolic health and thus your level of risk.” Mosconi agrees. Everyone, especially women in their 40s and 50s, should “know their numbers,” she says, meaning APOE status, metabolic profile, blood biochemistry—even brain scans, especially as new sex-specific imaging biomarkers emerge. “I hope scans will become part of the clinical workup for all middle-aged women (and men) for preventive reasons, just as we have our breasts and uterus checked,” she says. The mantra is “prevention,” a word once seldom paired with Alzheimer’s.

Whether HT should be part of a protocol remains controversial. But precision medicine—which uses genetic testing and data analytics—is coming to HT, Brinton says: doctors may soon prescribe precision therapies based on biomarkers of risk such as APOE status, reproductive history, menopausal symptoms, and other factors. And new versions of HT are in the works. Karyn Frick, a neuroscientist at the University of Wisconsin–Milwaukee, and her collaborators have developed a “stripped-down” version of 17β-estradiol that is thought to reduce the risk of breast cancer associated with standard HT. The drug, which has yet to undergo clinical trials, showed promise in preliminary studies in mice. “It acted as a memory enhancer,” Frick says.

For the Alzheimer’s cases that cannot be prevented, Brinton’s laboratory is developing a treatment called Allo based on allopregnanolone, a naturally occurring steroid that stimulates the production of new neurons. In a mouse model of Alzheimer’s, Allo reversed cognitive deficits and restored learning and memory. In a promising phase 1 clinical trial, patients with mild dementia showed regenerated gray matter volume in their hippocampus and a reduction in brain inflammation. Brinton says a phase 2 clinical trial with APOE4 carriers, funded by the National Institute on Aging, is scheduled to begin later in 2020.

In 2016 the National Institutes of Health began to require that the research it funds regard sex as a biological variable. The slow course of Alzheimer’s means that years will pass before women can benefit from new studies into the menopause transition. Meanwhile prevention remains essential: recommendations include a plant-centered diet that is low in sugar and in trans fats and saturated fats, physical exercise, stress reduction and a nightly seven hours of beta- and tau-clearing sleep, especially for women in midlife. “Women take care of others; we put ourselves last,” Brinton says. “But we can’t keep putting off health.”
THE ROLE OF AIR POLLUTION

Airborne particles spewed by car exhausts and other sources are now strongly linked to Alzheimer’s. Recent research shows how they can travel from the lungs and nose to the brain

By Ellen Ruppel Shell
My first day in Mexico City was tough. The smog was so thick that I gasped for breath while climbing the stairs to my hotel room. I had braced for headaches from the high altitude and thin air, but I was not prepared for how dirty that air was or for the bloodshot eyes and burning lungs.

Declared the world's most polluted metropolis by the United Nations in 1992, greater Mexico City has worked hard to clean up its act. To some degree it has: the city is rightfully proud of its miles of bike paths and lush parks. Yet a casual glance at the smudged horizon shows that those efforts are not enough. Most days the area has levels of airborne sooty particles that greatly exceed standards set by the World Health Organization, as well as elevated amounts of other pollutants. Clogged with more than 10 million vehicles and an estimated 50,000 smokestacks, Mexico City stews in a toxic brew known to corrode human lungs and hearts. Now many scientists agree that this pollution also damages the brain.

In 2018 a study found lesions known to be hallmarks of Alzheimer's disease in the brains of Mexico City residents in their 30s and 40s—decades before signs of the disease normally can be detected—and tied this damage to exposure to the city's bad air. The researchers who did that work, who are from institutions in Mexico and the U.S., have also found early signs of this frightening damage in infants and young children. And Mexico City is not the only place where bad air has been linked to Alzheimer's. Just a few years ago a team of Harvard scientists released data from a large study of 10 million Medicare recipients ages 65 and older living in 50 different cities in the northeastern U.S. The researchers reported a strong correlation between exposure to specific air pollutants and a number of neurodegenerative disorders, including Alzheimer's.

Other studies in England, Taiwan and Sweden—among other countries—have turned up similar results. "Air pollution is emerging as one of the hottest areas in Alzheimer's research," says George Perry, a neurobiologist at the University of Texas at San Antonio and editor in chief of the Journal of Alzheimer's Disease. In a field where scientists have spent decades focused on genetics and the buildup of damaged protein fragments called beta-amyloid as causes of the disease, Perry says, now many experts agree that air pollution plays a major role. This assessment is echoed by Masashi Kitazawa, a toxicologist at the University of California, Irvine, and an expert on environmental toxins. "Genetics is huge in Alzheimer's research, and for years almost no one wanted to look beyond genes," he says. "But in the past three or four years the number of papers linking air pollution and cognitive decline has exploded." For the most common form of Alzheimer's, known as late-onset disease, researchers now estimate that at least 40 and as much as 65 percent of the risk involves nongenetic influences such as lifestyle and harmful environmental exposure. Air pollution is one of the leading factors.

Much of this concern centers on airborne toxic-packed droplets or solid bits that are about one 30th the diameter of a human hair. Known as fine particulate matter (called PM 2.5 for its specific size), it typically comes from burning oil and gas in cars and trucks and power plants, as well as from burning coal or wood. These particles are inhaled deep into the lungs and can pass quickly into the bloodstream. Scientists have demonstrated that when PM 2.5 enters the body this way, it wreaks havoc on human respiratory and cardiovascular systems, leading to cancer, heart attacks, strokes and early deaths.

Scientists once thought that the brain was protected from similar carnage by the blood-brain barrier, a network of closely packed cells lining blood vessels of the brain that prevents toxic substances from passing from the blood into brain tissue. Unfortunately, there is now compelling evidence that PM 2.5 can and does enter the brain via two pathways. First, the particles can alter the blood-brain barrier itself to make it more permeable to pollutants. Second, the particles can bypass the barrier altogether by slipping from the nose into the olfactory nerves and then traveling to a part of the brain called the
olfactory bulb. The brain, it turns out, is no more protected from the relentless assault of air pollution than is any other organ.

**HIGH EXPOSURE**

Much of the recent work linking poor air quality and brain disease has its roots in the early research of Lilian Calderón-Garcidueñas, a physician and neuropathologist at the University of Montana. Born and raised in a town not far from Mexico City, Calderón-Garcidueñas has studied the health impacts of the region’s foul air for decades. In the early 2000s she examined 40 dogs roaming the most polluted parts of Mexico City and found Alzheimer’s-like pathology in their brains. This discovery prompted her to look at the brains of humans who had lived in similar neighborhoods. What she saw—Alzheimer’s-associated proteins in the brains of children and infants as young as 11 months—alarmed her. “Exposure to air pollution,” she wrote in 2008, “should be considered a risk factor” for Alzheimer’s, in particular for those who are genetically predisposed to the disease.

Calderón-Garcidueñas’s conclusions have been substantiated by other scientists. Jennifer Weuve, associate professor at the Boston University School of Public Health, led one of the first U.S.-wide investigations into the link between air pollution and brain disease and published the results in 2012. “We had two hints on the relationship between the aging brain and air pollution,” she says. “The first was the impact of air pollution on the cardiovascular system—heart attacks and strokes. The brain relies on blood circulation, so naturally this raised concern that the brain, too, was being affected. The second hint was subtler. Toxicologists did some well-controlled studies of animals exposed to air with high levels of suspended particles and found that these particles got into the brain. Some of those particles contained known neurotoxins, like manganese. And we knew that couldn’t be good.”

More epidemiological evidence of an airborne-particle problem has since piled up. In 2018 the BMJ published a study of some 131,000 London residents aged 50 to 79 and concluded that those with the most exposure to air pollution were the most likely to be diagnosed with dementia over the eight years they were observed. The link was particularly strong between Alzheimer’s and PM 2.5 particles. A study of nearly 100,000 residents of Taiwan found similar results. Researchers in Sweden concluded that air pollution increased dementia incidence even among people with no genetic markers for the disease. And scientists at the University of Toronto looked at 6.6 million people in the Canadian province of Ontario and found that those who lived within 50 meters of a major road, where levels of fine pollutants are very high, were 12 percent more likely to develop dementia than individuals living more than 200 meters from those same roads.

**FROM AIR TO BRAIN**

Of course, epidemiological studies have limits. It is unethical to ask humans to knowingly expose themselves to polluted air over a period of months or years. This restriction makes it difficult to carry out controlled studies that eliminate many factors other than air pollution that might predispose residents of some regions to Alzheimer’s and other forms of dementia.

“In a perfect world, everyone would wear an air-pollution monitor so that we could get real-time data on their exposures,” Weuve says. “But this is not a perfect world. So we work with experts to build estimation models. It’s not enough. In the case of Alzheimer’s, it’s chronic, long-term exposure that counts, and we don’t even have a worldwide registry of people with Alzheimer’s, let alone the resources to follow people for many years prior to their acquiring the disease. So it is quite difficult to nail down causation.” Indeed, in some regions of the world, air pollution is so bad that people die of heart disea-
A study published last year found clear links among fine-particle pollution, structural changes in the brain and memory loss in older women.

reported that heavy metals from polluted air not only found their way into the brains of rats after just a few months but also appeared to activate genes that trigger neurodegenerative disorders and cancer.

Air pollution might also interact directly with variants of certain genes associated with Alzheimer’s, prompting the acceleration of brain aging and neurodegeneration in people who are already genetically susceptible. Not all people with late-onset Alzheimer’s have these genetic markers, but many do, and the one-two punch of a gene-environment interaction seems to be particularly potent. Clinical psychologist Margaret Gatz of the University of Southern California explains that damage to the vascular system from pollution and other factors is associated with an increased risk of Alzheimer’s and other forms of dementia, especially in people who have a genetic tendency to acquire the disease. “There’s a good deal of evidence that vascular risk factors are more dangerous for carriers of the APOE4 variant of the APOE gene,” she says. “And for this and other reasons, a lot of research has focused on the genetic risk of the disease and all but overlooked the lifestyle and environmental component.”

What toxic substances found in air pollutants do when they get to the brain fits well with several ideas about the way Alzheimer’s-related damage develops. Neurotoxicologist Deborah Cory-Slechta of the University of Rochester Medical Center says that in both animals and humans, these pollutants prompt the release of cytokines from microglia cells, the resident immune sentinels in the brain. Cytokines are signaling molecules that help to regulate immunity and inflammation. Under normal circumstances, this response can help protect the brain against outside invaders. But chronic exposure to polluted air can result in the overproduction of proinflammatory cytokines and chronic inflammation that leads to nerve cell death. “Ultrapine particles seem to be the most important factor in this process,” Cory-Slechta says.

She also notes that it is hard to zero in on specific components of these particles. “For one thing, we have very little historical data on them, so it’s hard to judge their relative levels in the environment. For another, they contain lots of different substances that we tend to clump together,” making it difficult to know what specifically is causing the negative effect.

Particle pollution from the burning of fossil fuels and other sources contains hundreds of substances, ranging from noxious gases such as sulfur dioxide and nitrogen oxides to the dust emitted from automobile and truck brakes, tires and clutches. Cory-Slechta says that these pollutants tend to accumulate in the brain over many years, which might help explain why Alzheimer’s is typically a disease of old age. But, she adds, there are still many unknowns about what exactly gets into the brain from the air—it’s not clear that all these substances make it inside—and when those that do cause trouble. “What we do know is that iron, zinc, copper, and other metals are required by the brain, but at a specific level. What happens when that level is exceeded?” she asks. “We know that too much iron can lead to oxidative stress and neurodegeneration. We also know that some pollutants, like aluminum, play no essential role in the brain yet tend to accumulate there and provoke an inflammatory response. Frankly, I think we should be taking a closer look at that. And it’s not just metals. Organic contaminants might also be involved in neurodegenerative disease.”

One type of such organic pollutants are lipopolysaccharides, large molecules released from bacteria spewed from waste-treatment plants and other sources. Scientists have found these molecules can latch onto particulates and, when inhaled, provoke an inflammatory response in the lungs. In animal studies, lipopolysaccharides and other organic matter have also been shown to provoke inflammation and related cognitive degeneration in the brain.

PARTICLES AND MEMORY LOSS

JIU-CHUAN CHEN, a physician and epidemiologist at the University of Southern California, specializes in the study of airborne pollutants in the brain and says that although the impact of individual substances is still under debate, the overall effect of the mix is clearly related to brain damage and cognitive problems. Chen was co-author of a study published last year in the journal Brain that found clear links among fine-particle pollution, structural changes in the brain and memory loss in older women. Chen and his collaborators used
neuroimaging and cognitive tests to measure brain changes and memory, plus a mathematical model that incorporated two sources of environmental air-quality data.

“We found that women with the highest exposure to pollutants showed an early decline in episodic memory,” he says. This type of long-term memory involves recalling a previous experience along with the time and place of the event and associated emotions. The decline Chen detected in these women appeared preclinically—before any actual symptoms of Alzheimer’s—and was independent of the subjects’ cardiovascular status. Alzheimer’s research has established that people with a decline in episodic memory have a very high risk of developing the full-blown disease later in life.

“There are more than 10 studies that link late-life exposure to air pollution and dementia,” Chen says. “The evidence is quite compelling. Whether exposure in early life is also a factor, we don’t know. But in animal studies, toxicologists start exposure in early life, look at the pathological changes and see problems. It looks like small particles can accelerate the amyloid-deposit process, but we’re not yet sure whether this happens in humans. And there might be a genetic component involved—that is, some people might be more susceptible than others to the effect of pollution. There might be a subgroup of individuals who are particularly susceptible and might be at greater risk. We don’t yet have enough power in our studies to address this question, but I believe we will.”

RISK REDUCTION

While the disease remains a horror facing millions of people around the globe, there is some encouraging news in these discoveries about air pollution, several scientists say: people can take action to diminish the hazards. Most drugs so far have not helped patients, says George Washington University epidemiologist Melinda Power, who focuses on identifying modifiable risk factors for cognitive decline and dementia. “So at the moment, prevention through the reduction of environmental and lifestyle factors looks like our best bet,” she says. “And air-pollution exposure is looking like it could be very important.”

The evidence about brain damage is a strong argument for stricter air-quality controls, says University of Michigan epidemiologist Kelly Bakulski. “This is a really hopeful area,” he says. “Unlike our genes, environmental factors are things we can control—removing these pollutants from our communities will have no ill and many positive impacts.”

In addition, Gatz says that simple changes in how we live can help. “Physical exercise is shown to reduce risk,” she says, both because it increases blood flow to the brain and because it increases levels of brain-derived neurotrophic factor, a protein that promotes the growth and maintenance of brain cells.

Knowing the havoc that the disease inflicts, it is time to take such changes seriously. “We have the means to do it,” Bakulski says, “and given the risk of not doing it, we must.”

More to Explore on Alzheimer’s Disease

Research papers and archival coverage related to the articles in this special report.

“The Way Forward”
From Our Archives

“The Menopause Connection”
From Our Archives
Preventing Frailty. By Sonia Minikel Vallaah and Eric Vallaah Minikel; March 2020.

“The Role of Air Pollution”
Alzheimer’s Disease and Alpha-Synuclein Pathology in the Olfactory Bulbs of Infants, Children, Teens and Adults ≤ 40 Years in Metropolitan Mexico City: APOE4 Carriers at Higher Risk of Suicide Accelerate Their Olfactory Bulb Pathology. L. Calderón-Garcidueñas et al. in Environmental Research, Vol. 166, pages 348–362; October 2018.
Particulate Matter Air Pollution, Physical Activity and Systemic Inflammation in Taiwanese Adults. Z. Zhang et al. in International Journal of Hygiene and Environmental Health, Vol. 221, No. 1, pages 41–47; January 2018.
From Our Archives
The Metabolism of Cities. Abel Wolman; September 1965.