Environmental Threats to Healthy Aging

With a Closer Look at Alzheimer's & Parkinson's Diseases

Greater Boston Physicians for Social Responsibility

and Science and Environmental Health Network

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This report is dedicated to Maria Valenti by her co-authors with gratitude for her tireless, inspiring work for peace, justice, health, and the environment.

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Greater Boston Physicians for Social Responsibility
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GBPSR is a chapter of Physicians for Social Responsibility, a national nonprofit organization of over 30,000 health care professionals and supporters who are committed to the elimination of nuclear and other weapons of mass destruction and the preservation of a sustainable environment. PSR is the national affiliate of International Physicians for the Prevention of Nuclear War, the 1985 Nobel Peace Prize-winner. Since the early nineties GBPSR has been effectively working to educate the medical community, policy makers and the public about the health consequences of environmental degradation and exposures to toxic chemicals, and advocating for strategies to protect public health. Our research reports, Generations at Risk: Reproductive Health and the Environment (1996, and MIT Press, 1999), and In Harm's Way: Toxic Threats to Child Development (2000) have provided the scientific groundwork for advocacy campaigns to protect health, and have helped change public policies and clinical practice. We have educated thousands of health professionals through hundreds of education courses and presentations throughout the country and Canada at hospitals, clinics, and medical schools. We have continued to break new ground by developing clinical tools such as our Pediatric Environmental Health Toolkit, endorsed by the American Academy of Pediatrics. GBPSR remains committed to working to educate about the dangers of nuclear weapons, and the health effects of militarism and war.

The Science and Environmental Health Network
http://www.sehn.org

The Science and Environmental Health Network (SEHN) is a think tank engaging organizations, communities, and governments in the effective application of science to protect and restore public and ecosystem health. SEHN uses the concepts of ecological medicine and ecological health to address the nexus of science, the environment, and human and ecosystem health. SEHN is also a leading developer of theory, law, and practice based on the precautionary principle. Founded in 1994, SEHN operates as a virtual organization, currently with six staff members working across the U.S.

Table of Contents

A symbol of longevity in Japanese culture. Look for other symbols of health and long life throughout the book.

Foreword

A healthy brain is absolutely essential for successful, healthy aging. The brain is the center of thought and the seat of emotion. The brain is responsible for receiving, interpreting, and organizing data from the senses; formulating speech; guiding action; storing memories of the past; and planning strategies to shape the future. The brain directs all of our dealings with the world around us and all of our interactions with the people whom we love.

When the human brain is afflicted by degenerative conditions such as Alzheimer's disease, other forms of dementia, or Parkinson's disease, quality of life is severely diminished. In persons with Alzheimer's disease, memory is lost, speech becomes impaired, and interactions with the world are constricted. In persons with Parkinson's disease and amyotrophic lateral sclerosis, cognition is preserved, at least for a while, but movement is impaired, fine motor functions are degraded, walking becomes difficult, and even the ability to breathe can be lost.

When the human brain is afflicted by degenerative conditions... quality of life is severely diminished.

Alzheimer's disease and Parkinson's disease are the two most common neurodegenerative diseases of the older American population, and they profoundly threaten healthy aging. Causation of these diseases is complex. In a minority of cases, particularly in those with onset before age 50, causation appears to be largely genetic. But in most cases, causation appears to involve still poorly understood interactions among multiple genetic and environmental factors. Lead and PCBs are among the environmental agents that have been linked to dementia. Parkinson's disease has been linked with exposures to the synthetic heroin MPTP, the pesticide rotenone, and the metal manganese. It seems very likely that many other modern synthetic chemicals, the majority of which have never been properly tested for neurotoxicity, may also be potential causes of neurodegenerative diseases, and research to establish these associations is urgently needed. In addition to chemicals, nutrition and socioeconomic circumstances seem to influence the risk in many people. Social isolation and inadequate access to healthy food are toxic to the aging brain and are all too common in today's world.

Information is emerging that exposures sustained in the earliest stages of life—even in the womb and in the first years after birth—may have the potential to initiate changes in the brain that, decades later, result in Alzheimer's disease, Parkinson's disease, or other forms of neurological degeneration. This "early origins hypothesis" was first proposed by Professor David Barker of the University of Southampton in the UK in studies of the antecedents of heart disease and diabetes. Professor Barker found that infants with low birth weight and small head circumference are at increased risk as adults of developing coronary heart disease, hypertension, stroke, insulin resistance, and diabetes. He found that reduced fetal growth and impaired development during infancy are associated

The whale symbolizes longevity in Native American mythology

This book is a "must read." While it emphasizes the importance of research to understand the origins of neurodegenerative diseases, it also calls for action.

with increased mortality from cardiovascular disease across the entire lifespan. More recently, information on early life exposures to toxic chemicals such as lead, mercury, pesticides, and PCBs has extended the early origins hypothesis to encompass chemical exposures. This research suggests that early chemical exposures may result in a range of diseases in childhood and throughout the lifespan, including diseases of the central nervous system such as reductions in intelligence, shortening of attention span, and disruptive behavior. Animal studies suggest that early exposure to a combination of two herbicides—maneb and paraquat—may accelerate development of Parkinson's disease. These discoveries establish the concept that environmental exposures can produce degenerative disease of the brain. The task now is to identify additional causal exposures, so that evidence-based programs of prevention can be launched.

This important book from Greater Boston Physicians for Social Responsibility and the Science and Environmental Health Network presents in clear, balanced, and understandable terms the emerging evidence that toxic environmental exposures, in combination with nutritional, social, and exercise variables, contribute to the causation of Alzheimer's disease, Parkinson's disease, and other chronic degenerative diseases of aging. It offers prudent suggestions in light of current knowledge for reducing exposures and building resilience against environmental threats.

This book is a "must read." While it emphasizes the importance of research to understand the origins of neurodegenerative diseases, it also calls for action. Urgently needed reforms include requiring safety tests for industrial chemicals before marketing; providing incentives to produce and market healthy food rather than products that contribute to chronic diseases; reducing or eliminating emissions that accelerate chronic disease and climate change; and emphasizing disease prevention in healthcare policies. These are essential to confront the public health threats facing the U.S. and many other countries of the world, but they are not enough. Every economic sector, school district, city council, hospital, legislature, community, family, and individual has a role to play. This book is important today, and it will become increasingly important in the years ahead as the number of elderly among us continues to increase.

I highly recommend this book for physicians, nurses, and other healthcare providers as well as for policy makers and the general public. It is readable at every level. It is a treasure house of important information.

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Executive Summary

A dramatic increase in the aged population in the United States over the next few decades is expected to nearly double the number of people 65 and over by 2030. This "age wave," fueled in the United States by the baby boomers, will soon reach shore and influence almost all aspects of our lives, including health care, economics, and social structure. Improved longevity is a success story and offers exciting opportunities, but at the same time it poses tremendous challenges. Among them are the growing threats of chronic diseases associated with aging and their changing patterns.

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This report primarily examines the lifetime influences of environmental factors on Alzheimer's and Parkinson's diseases and their underlying pathologic mechanisms. Our close look at the science of these diseases shows they are related to a number of features of modern society and that Alzheimer's disease especially is linked to other serious health problems of modern times, which we call the "Western disease cluster."

By environment we mean the entire physical, biological, social, and cultural context in which we live, from conception to death. We take an ecological perspective since individuals do not live in isolation but as members of families, communities, and natural systems. Our findings show that a complex mixture of variables at each level influences the health of individuals and disease patterns in populations. If we do not confront them comprehensively, we risk overwhelming the health care system and weakening the social and economic fabric of families and communities.

The pear is a symbol of hope and good health in many cultures. The Chinese associate the image with longevity, justice and good judgement.

A Multifactorial, Lifespan Perspective Points to Opportunities for Prevention

- Beginning in the womb and continuing throughout life, environmental factors are strong determinants of health decades later. The course of brain development follows an arc that begins soon after conception and progresses along some trajectory into

adulthood and older age. The shape of that trajectory—its features, length, and rate of change—can be profoundly influenced by many interacting genetic and environmental factors encountered throughout the lifespan. Early life events or circumstances can have enduring impacts on brain aging and function.

- Brain "reserve" or resilience can influence the timing of onset and progression of neurodegenerative conditions. They may be delayed in people with more reserve and accelerated in those with less. Brain reserve may be influenced by modifiable environmental variables, beginning with early development.
- Many "neurodegenerative" diseases might best be considered as existing along a continuum rather than as discrete, unrelated entities. A spectrum could better reflect the mix of symptoms and histopathologies seen in many cases that sometimes make it difficult to settle on a single diagnosis. A spectrum might also better accommodate diverse mechanistic biological pathways, influenced by interacting environmental and genetic variables, which may then converge into final common pathways and result in clinical disease. With respect to cognitive decline, disease severity can also be seen along a spectrum running from normal aging to dementia.
- It is highly likely that for many people, development of the two most common neurodegenerative diseases, Alzheimer's and Parkinson's, can be delayed or prevented altogether. In most cases these diseases result from the interaction of a number of different factors. They must be understood within a framework that includes biologic, social, economic, and cultural dimensions. These dimensions are represented, in turn, at all levels from the sub-cellular to society as a whole. The presence of certain genes may increase the risks of these diseases, but the actual pathologic processes leading to these conditions can also be highly influenced by environmental factors.

Underlying Dimensions of Neurodegenerative Disease

- Common mechanisms and pathways underlie many prevalent disease patterns. At the micro-level, inflammation and excessive oxidative stress play critical roles in the development and progression of Alzheimer's and Parkinson's diseases. Diabetes, obesity, hypertension, elevated blood lipids and metabolic syndrome are also often characterized by inflammation and excessive oxidative stress. They also tend to co-occur in individuals and in large populations, particularly as they undergo modern industrialization.

We refer to this group of chronic diseases as the "Western disease cluster." Substantial evidence suggests that common forms of dementia—including Alzheimer's and vascular dementia—are associated with this cluster as well.

- Recent scientific advances reveal connections among inflammation, oxidative stress, and disrupted insulin signaling pathways. The consequences of disrupted insulin signaling include insulin resistance, elevated glucose, vascular disease, and elevated blood lipids—key factors in the Western disease cluster. Environmental influences that may contribute to inflammatory disruption of insulin-signaling include toxicants, inflammatory nutrition patterns, inactivity, obesity, psychosocial stress, and various health conditions.

An individual's or community's position on the socioeconomic gradient is one of the strongest determinants of health status.

Environmental Risk Factors in the Development of Dementia/Alzheimer's & Parkinson's Diseases

- Modifiable lifetime environmental factors that influence aging and health include nutrition; exposure to environmental chemicals and infectious materials; physical activity; social interactions; education; socioeconomic circumstances; and active intellectual stimulation. These factors do not act in isolation. Rather, they interact and collectively, along with multiple genetic influences, create the conditions out of which health or disease emerge.
- Individual lifestyle choices can influence which environmental factors will affect disease risk. However, lifestyle factors are not simply matters of individual choice. They are highly influenced by availability, cost, advertising and cultural preferences among other factors. Consequently patterns of disease are not simply the product of individual choice but are also features of families, communities and societies. Indeed, drivers of excessive inflammation and oxidative stress are present at all levels of the eco-social environment. Disease prevention requires public health approaches as well as healthy lifestyle choices.
- An individual's or community's position on the socioeconomic gradient is one of the strongest determinants of health status. Lower socioeconomic circumstances are associated with increased risk of disease and premature mortality at every level of the gradient. All diseases of the Western disease cluster are over-represented in people of lower socioeconomic status.
- A coherent and growing body of evidence indicates that numerous nutritional factors—especially in combination—can increase the risk of neuroinflammation, excessive oxidative stress, and

Our task is not only to respond to the medical and social needs of individual people who are sick or at risk, but also to optimize conditions so that fewer people find themselves at risk in the first place.

neurodegeneration. These nutritional factors include consumption of saturated and trans fats and refined carbohydrates, along with inadequate intake of omega-3 fatty acids, antioxidants, and micronutrients. This dietary pattern stimulates an inflammatory response in many tissues and organs, mediated in part by the innate immune system. It can also increase the risk of Western disease cluster illnesses as well as neurodegenerative disease.

- The dominance of this inflammatory nutrient pattern results, in significant degree, from trends in agriculture, food production and marketing over the past 50–100 years. These trends include the growth of factory farming and consumption of fast foods and highly processed foods. These trends in food production and distribution have also intensified dependence on fossil fuels. This adds to chemical and climate impacts, compounding risks to human and ecosystem health.
- Many environmental chemicals promote excessive oxidative stress and inflammation and contribute to the risk of neuroinflammation and neurodegeneration. Environmental chemicals can also modify gene expression and alter brain development through a variety of mechanisms, increasing the risk of neurodegenerative diseases later in life. Chemicals of concern include lead and other heavy metals, PCBs and other persistent organic pollutants, and pesticides. Endocrine disruptors to which the population is widely exposed also have inflammatory and metabolic effects. Bisphenol A, for example promotes insulin resistance and the accumulation of fat at relatively low levels of exposure. Exposures to PCBs, dioxin, and several pesticides also strongly correlate with the likelihood of having type 2 diabetes, insulin resistance, and the metabolic syndrome. Emerging evidence also suggests that air pollution contributes to brain inflammation and the risk of Alzheimer's-type neurodegenerative disease.

Human and Ecological Health are Interdependent – Cross-Cutting Solutions are Possible

Changes in the natural, built, and social environments during the 20th century in the U.S. and many other countries strongly contributed to increased life expectancy and other indicators of human development. But many changes also altered system conditions so that large numbers of people are living close to or beyond

thresholds of chronic diseases that severely undermine quality of life. Upward age-adjusted trends in obesity, diabetes, hypertension, asthma, and some kinds of cancer are illustrative. Our task is not only to respond to the medical and social needs of individuals who are sick or at risk, but also to optimize conditions so that fewer people find themselves at risk in the first place.

As the evidence in this report demonstrates, key elements of healthy living include:

- Eating healthy and nutritious food;
- Staying active physically and mentally;
- Avoiding harmful toxicants and pollutants;
- Being socially engaged with family, friends, and community.

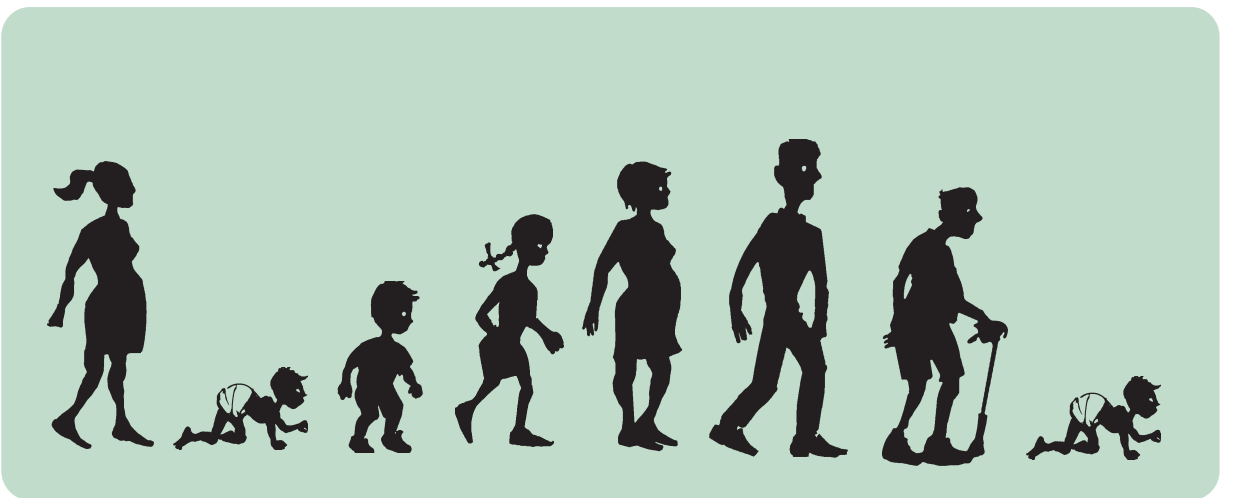
Individually and collectively these approaches can reduce excessive oxidative stress, inflammation, and other pathogenic biologic pathways, and help to reduce the risk of obesity, overweight, dementia and diseases of the Western disease cluster.

Individual actions are not enough. In multifactorial diseases, policy interventions at many levels are necessary and can have profound influences on individual and population health. Some policy interventions are cross-cutting, addressing multiple risk factors simultaneously. For example:

- Encouraging more localized, diversified and sustainable food production rather than factory farming would enhance nutrition, decrease the environmental impacts of agriculture, and strengthen local economies. It would reduce reliance on pesticides and minimize the use of fossil fuels for long distance transport. This in turn would reduce air and water pollution as well as greenhouse gas emissions.
- Transitioning to clean, renewable energy and reducing fossil fuel consumption in general would drastically reduce air pollution, which is increasingly recognized as pro-inflammatory, neurotoxic, and contributing to cardiovascular disease. It would also undercut a host of harmful chemical exposures related to production, transport, and use of fossil fuels. Prioritizing the development of energy-efficient mass transit systems that interface with bike paths and sidewalk networks would save energy while minimizing air pollution and combating obesity.

- Reducing use of toxic substances in the home, workplace, and community through "safer substitute" programs and green product design can reduce exposures that contribute to neurodegeneration and many other chronic diseases, reduce ecosystem and wildlife contamination, and create new jobs.
- Reducing socioeconomic disparities and making certain that all people have access to affordable health care, as a right and a matter of decency, will reduce the general chronic disease burden and help to alleviate its consequences for individuals and society.

Much of the chronic disease burden could be reduced by addressing the broad environmental-context of health, and prioritizing primary prevention at many levels—from the individual to the family, community, society, and ecosystem. Throughout the lifecycle our health is deeply connected to other stages of life, and to the ecosystems around us that are literally our lifeblood. Fortunately, we have innumerable opportunities to jointly improve health throughout the lifecycle and to restore degraded ecosystems. In so doing we can achieve human and ecological health that are interdependent, urgently needed, and within our reach.



Aging begins at conception.

Chapter 1

Aging and Health: Challenges and Opportunities

An Age Wave Heads to Shore

Social scientists have been monitoring with great interest an approaching tidal wave that may well overwhelm the resources of the United States and many other countries if we don't carefully plan for it. This wave will nearly double the number of Americans 65 and older from about 38 million today to over 71 million by 2030.[1] And it carries with it a whole collection of age-related health concerns.

Increased longevity is a success story with many heroes, but the trend poses tremendous challenges. Innovations in healthcare delivery, housing, land-use planning, transportation, agriculture, food distribution, and other societal activities will attempt to respond to the demographic shift, competing with other needs of the 21st century. Ethical questions concerning how and where elders fit into society and our responsibilities to them as well as future generations will take on new dimensions.

The boomers' history of tackling thorny challenges and reinventing themselves regularly as they move through life could presage widespread innovation in approaches to healthy aging. Enormous benefits could accrue to societies when this huge former labor pool becomes available for volunteerism. Intergenerational relationship building could once again expand. Indeed, many are hoping that the generation responsible for many dynamic technological advances will help develop new ways to address looming age-related health concerns.

THE ONCOMING AGE WAVE is fueled in part by the "baby boom" generation (Americans born between 1946 and 1964). In 2000, people over 65 represented a little over 12 percent of the population and this is expected to grow to nearly 20 percent by 2030. The census bureau predicts that the over-85 age group alone will almost double from nearly five million in 2003 to nearly ten million by 2030. This continues a dramatic demographic transformation that has doubled the older population in the U.S. every 30 years since 1900.[2]

This trend is also underway not only in other industrialized countries but also in the "global South" (less industrialized countries), where over half (59 percent) of the world's elderly (65 and over) lived in 2000. That proportion is expected to increase to over 70 percent or 686 million older people in developing nations by 2030. Older age groups will also continue to be a growing portion of the population in these Southern countries.[3]

The turtle image is a symbol of longevity in Native American cultures.

In the best of all worlds, a relatively healthy older population would actively continue to contribute to society while placing minimal additional demands on healthcare and care-taking resources. Setting this goal would prompt us to identify age-associated disorders that might be prevented or delayed, thereby compressing the illness burden into a shorter period of time near the age of death.

Thus, the pathway to healthy aging is lined with healthy pregnancies, infants, children, and adults.

The optimum aging scenario, says Andrew Weil MD, a pioneer in integrative medicine, is to remain as healthy as possible until we approach death, and then rapidly decline: "I don't subscribe to the concept of 'anti-aging' or the view that we can reverse the physical changes that come with growing older. However, I do believe we can age with grace, and that we should do everything in our power to delay the onset of age-related disease, discomfort and loss of vigor."[4] Peter J. Whitehouse MD, PhD, a geriatric neurologist at Case University and noted expert on Alzheimer's disease, agrees. He adds, "A lot of people are making money out of convincing people aging is a disease. It is not."[5]

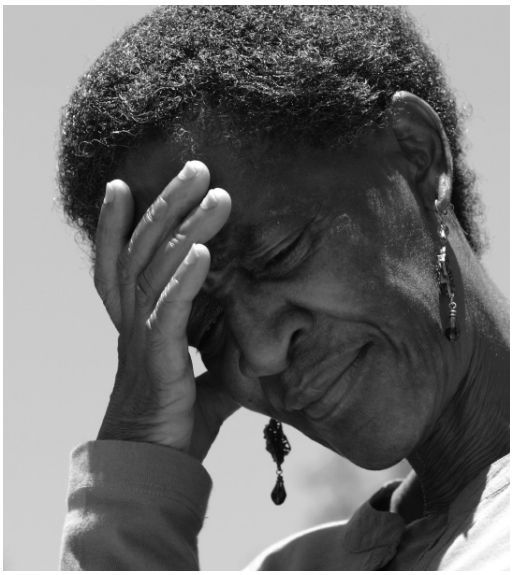
The Origins of Chronic, Degenerative Diseases

The material developed in this report stems from our long-term interest in the relationships connecting human health and the environment. By environment we mean the entire physical, biological, social, and cultural context in which we are conceived, born, grow, age, and die. In recent years, influences of chemical exposures, inadequate or inappropriate nutrition, and socioeconomic stress on children's health have received much-needed attention as critical components of the environment. Scientists tell us about the unique vulnerability of the developing child to each of these.

We have also wondered how these variables might influence the health of older people. This, too, is a vulnerable stage of life. As it turns out, we now know that environmental influences beginning in the womb and continuing throughout life are strong determinants of health decades later. That is, health in older age is, to a large extent, a reflection of health throughout life, beginning with conception. Thus, the pathway to healthy aging is lined with healthy pregnancies, infants, children, and adults.

The challenges in assessing the impacts of chemical exposures, diet, social status, and other environmental factors on health in later years are unique. Children grow, develop, and

acquire functions and skills. Older people lose many of them. Normograms of child development, which help parents and clinicians track growth and acquisition of age-appropriate skills, do not have their counterpart in the aged. But, like delayed or slowed child development, combinations of early onset or accelerated progression of functional decline in older people are more likely to draw medical attention. Still, the line differentiating normal aging from disease is often indistinct. Where it is drawn can be determined as much by social convention as by biology. And where it is drawn helps to set the stage for individual or societal responses.



Over time, disease patterns change. Fewer infants and children now die of infectious diseases than at the beginning of the 20th century, but more are afflicted with birth defects, asthma, cancer, diabetes, and obesity. Among adults, cardiovascular disease, cancer, and diabetes are now leading causes of morbidity and mortality. But why do some people live relatively healthy lives until close to the time of their deaths, while others suffer with often debilitating chronic disease as adults? Can this be explained by genetics, personal behavioral patterns, and luck? Are there also features of the shared environment beyond individual control that help to explain these disparities as well as disease patterns?

Because health in the later years of life strongly depends on health in earlier years, this project is a logical extension of our 2000 report, *In Harm's Way: Toxic Threats to Child Development*. There we focused primarily on the impacts of toxic chemical exposures on the developing brain. Later we wondered if brain function might similarly be affected later in life and decided to focus primarily on the two most common neurodegenerative diseases—Alzheimer's disease and Parkinson's disease. These are chronic diseases that profoundly affect individuals, families, communities, and society. People with dementia have lost more than their cognitive ability. They have lost their personhood before losing their lives. People with Parkinson's disease live with more than shaking limbs and a stiff, unsteady walk. When they can no longer express their emotions on their faces they have lost essential ways of communicating with lovers, families, friends, and others.

People with dementia have lost more than their cognitive ability. They have lost their personhood before losing their lives.

The discussion in this report is relevant to a number of other diseases as well. It also speaks volumes about the state of the environment. In essence, we identify direct connections between the health of people and the health of the planet. From a public health perspective, much abnormal loss of neurological function in older people, as well as many increasingly common chronic diseases, is

PORTRAITS *of* AGING

It's morning in the Alzheimer's unit of the local nursing home. Behind the locked doors, the volume in the hallway begins to rise. One woman sings the refrain of a Christmas carol over and over, although the month is July. A man repeatedly shouts from his bed, "Where's my ticket?" Another complains that someone has stolen his cows. A night shift nurse, finishing up her paperwork, warns a morning nurse about the new patient in 3B. He was agitated all night and tried to kick his window out again. Claiming to be a prisoner of war, he appears delusional.

Out in the day room, two men, heads bowed, shuffle back and forth in the gait characteristic of Parkinson's disease. A woman bangs her wheelchair over and over into the corner of the wall. She will do this until someone turns her chair around. And then she will roll to the opposite corner of the room and bang some more.

The staff prepare cups of "thickened water" for residents who are losing their ability to swallow. This helps prevent aspiration. A room at the end of the hall is being prepared for the long-time resident in 9A. She has lost her swallowing reflexes altogether. Her grown children have been summoned and, once they arrive, they will be ushered into the new, quieter room to await the inevitable.

Taped to each door along the hallway is a photograph of the occupant and a brief biography that includes former hobbies and the names of family members both living and dead. The photos are intended to help residents find their rooms after meals. The biographies help the staff to converse with and calm the patients. Many occupations are represented among the residents: farmer, college professor, ballroom dancer, church organist, machinist, banker.

After his breakfast, the former banker wanders down the hallway. He stops to examine one of the photos. It is a picture of himself. He scowls and jabs his finger at the image. "Who is that guy?" he demands to know. "Who is that guy?"

These are not portraits of normal aging.

Contributed by Sandra Steingraber

Alzheimer's and other forms of dementia are major contributors to the rapid increase in demand for long-term care services.

linked to the profound changes brought about by humans in ecosystems throughout the world. The good news is that restorative win-win alternatives could lead to long-term sustainable health for both people and the planet.

Alzheimer's Disease and Parkinson's Disease

Changes in cognitive abilities, including attention, memory, and executive function, are common in normal aging. Healthy individuals are able to adapt by recruiting the services of other areas of the brain and are generally able to maintain adequate functional status. Yet, in some people, more rapid decline in the function of certain areas of the brain results in symptoms that ultimately lead to a diagnosis of Alzheimer's disease or Parkinson's disease. Although advancing age is the largest risk factor for each, their debilitating symptoms are not an inevitable feature of normal aging.[6]

The most prominent symptoms of Alzheimer's disease result from involvement of parts of the brain that control thought, memory, and language. Ultimately a person with Alzheimer's disease is unable to carry out daily activities independently. Functional decline accelerates, progressing to death. The disease usually becomes apparent after age 60, although it may have its origins many years before. Earlier onset of symptoms occurs but is uncommon. The risk of Alzheimer's disease increases with age. About 5 percent of all men and women ages 65–74 have Alzheimer's disease, while nearly half of those age 85 and older may have the disease.[7] Alzheimer's disease is estimated to affect nearly 4.5 million people in the U.S. This is expected to nearly triple by mid-century to over 13 million.[8] Worldwide, according to a 2007 World Health Organization report, Alzheimer's disease affects 24 million people.[9]

US-wide Initiatives on Aging

Below is a brief historical timeline of important initiatives on aging and health:

1945 - Harry Truman asks Congress for legislation that would establish a national health insurance plan. The issue is debated for twenty years, with opponents warning of the dangers of "socialized medicine."[1]

1958 - Dr. Ethel Percy Andrus, a retired high school principal, founds AARP. This evolved from the National Retired Teachers Association (NRTA), which Dr. Andrus had established in 1947 to promote her philosophy of "productive aging," and in response to the need of retired teachers for health insurance.[2]

1965 – President Lyndon Johnson as part of his "Great Society" enacts Medicare, providing health benefits for the first time to those over 65. Ex-president Truman is the first to enroll in Medicare. [3]

1985 – Environmental Protection Agency (EPA) and National Institute of Environmental Health Sciences (NIEHS) ask National Academy of Sciences (NAS) to investigate effects of the environment on elders.

1987 – NAS publishes *Aging in Today's Environment.*

2002 – EPA sponsors forum at the NAS, "Differential Susceptibility of Older Persons to Environmental Hazards."

Disease patterns change in response to historical forces, including interconnected environmental conditions and many kinds of human activity.

Parkinson's disease is a progressive disorder that includes combinations of tremors, stiffness, and emotional changes that ultimately lead to severe disability. About 50,000 new cases of Parkinson's disease are reported annually in the U.S. alone.[10] The number of individuals with Parkinson's disease over age 50 in the world's 10 most populous countries in 2005 is estimated at over 4 million. Prevalence of Parkinson's is expected to double by 2030.[11] These are estimates, as no comprehensive Parkinson's disease registries currently exist.

Socio-Economic Implications

The Alzheimer's Association estimates that national direct and indirect annual costs of caring for individuals with Alzheimer's disease are nearly $150 billion.[12] According to a recent study, the cost of caring for a person with Alzheimer's disease more than doubles over four years of care.[13] The cost of Parkinson's disease in the U.S. alone is estimated to be $13–28.5 billion per year.[14] Patients with both dementia and Parkinson's disease have significantly higher annual direct costs than patients with Alzheimer's disease alone.[15]

Alzheimer's and other forms of dementia are major contributors to the rapid increase in demand for long-term care services. Alzheimer's disease also dramatically affects the quality of life of family caregivers.[16] The majority of dementia-related deaths in the United States occurred in nursing homes (66.9 percent). In contrast, older persons with cancer mostly died at home (37.8 percent) or in the hospital (35.4 percent). The hospital was the most common site of death for all other conditions (52.2 percent).[17]

The World Health Organization's 2007 report on the global burden of neurological disorders shows that Alzheimer's disease and Parkinson's disease are more prevalent in higher income regions and account for a larger fraction of the disease burden. For example, Alzheimer's disease and other dementias constitute 1.47 percent and 2.04 percent of projected healthy years lost due to disease or disability in the Americas and Europe, respectively, compared to the African (0.10 percent) and Southeast Asian (0.26 percent) regions.[18] Even if much of this difference is attributable to more limited case ascertainment and higher prevalence of other diseases in some countries, it is dramatic. We examine cross-cultural studies more fully later.

A New Framework—An Ecological Approach to the Western Disease Cluster

Our interest in the origins and patterns of Alzheimer's disease and Parkinson's disease led us into expansive terrain encompassing many aspects of the natural, built, and social environments. It became clear that we needed to consider these diseases in a social, cultural, and historical framework while trying to understand their biological underpinnings. We also found links to a cluster of other diseases and conditions and, therefore, needed to examine broader disease patterns and even the way that we name and classify diseases.

Disease patterns change in response to historical forces, including interconnected environmental conditions and many kinds of human activity. These patterns can change slowly or more rapidly as may happen during times of war, famine, natural disaster, economic collapse, or epidemic infectious disease.

While looking at the macro level, we also turned to the micro level of cells, cellular signaling pathways, and sub-cellular organelles. The chapters that follow attempt to lay out how these various pieces fit together. Briefly, historically rapid and accelerating changes in virtually all aspects of socioeconomic life in the U.S. and most other countries of the world over the past 50–100 years created the conditions for new disease patterns. We can see the impacts of these changing conditions in communities, individuals, tissues, cells, and DNA.

An expanding collection of research tools has enabled scientists to describe in some detail biologic processes at the micro level that are set in motion by human-environmental interactions. These processes include, for example, gene mutation, enzyme induction, oxidative stress, inflammation, changes in membrane permeability or cell-to-cell signaling properties, and hormone disruption. We have learned just how much our health or risk of disease depends on our biologic responses to what we eat, drink, and breathe; exposures to industrial and other chemicals; social circumstances; interactions with other biological organisms; and many other aspects of our environment.

In this document we frequently emphasize, among the many potential responses to environmental stimuli, the role of inflammation and oxidative stress in the origins of many diseases. From the outset we stress that these are natural biologic processes

2002 – EPA launches Aging Initiative to examine, among other things, environmental hazards the elderly may face—and to shape a planned National Agenda for the Environment and the Aging.

2003 – EPA Aging Initiative conducts public "listening session" forums around the country to solicit input on environmental issues of importance to elders.

2007 – The U.S. National Academies *Keck Futures Initiative* convenes *The Future of Human Healthspan: Demography, Evolution, Medicine and Bioengineering* conference to provide a forum for interdisciplinary exploration of a wide range of challenges related to aging, and to propose innovative solutions.

Note: EPA references from Adler T. Aging research: the future face of environmental health. EHP. 2003 Nov; 111(14):A760-5 and Hood E. Toward a new understanding of aging. EHP. 2003 Nov; 111(14):A756-9.

1 Senior Journal. Available at: http://www.seniorjournal.com/NEWS/2000%20Files/Aug%2000/FTR-08-04-00MedCarHistry.htm. Accessed June 18, 2007.

2 AARP. Available at: http://www.aarp.org/about_aarp/aarp_overview/a2003-01-13-aarphistory.html. Accessed June 18, 2007.

3 Senior Journal 2000 op cit.

In a time of resource constraints, an overburdened healthcare system, and an approaching wave of age-related disease, preventing entire clusters of chronic debilitating illnesses should be a high priority.

that play essential roles in maintaining health. However, toxic chemical exposures, certain kinds of diets, and social stress, among other factors, can chronically up-regulate inflammation and oxidative stress so that they become initiators or promoters of disease. Indeed, as we will show, a coherent and compelling narrative links a number of environmental trends with abnormal up-regulation of these micro-level biologic processes. Moreover, inflammation and oxidative stress are key players not only in Alzheimer's disease and Parkinson's disease, but also in diabetes, cardiovascular disease, the metabolic syndrome, lipid disorders, obesity, asthma, and cancer. We do not mean to suggest that abnormal inflammation and oxidative stress are the only pathological processes of concern. But they are major pathways through which numerous environmental factors are integrated and contribute to a variety of chronic diseases. We will discuss this in some detail.

A Closer Look

Oxidative Stress

Oxidative stress occurs in the presence of highly reactive oxygen-containing compounds called "free radicals". Free radicals are an inevitable consequence of living in an oxygen-rich atmosphere and using oxygen to generate cellular energy. In fact, appropriate levels of free radical production are essential for health. But when free radical production is excessive or prolonged, oxidative stress is linked to the origins or progression of many diseases. (see chapter 6)

We call diabetes, cardiovascular disease, the metabolic syndrome, lipid disorders, and obesity the "Western disease cluster" because of their emergence as major public health concerns in Western society, their tendency to co-occur in individuals and populations, and their overlapping origins. We also note that this same cluster of conditions is becoming increasingly prominent in other countries, for example in India, as they modernize along pathways similar to the West.[19] We identify determinants of this cluster at every level from the societal to the sub-cellular and argue that those determinants play a role in the origins of Alzheimer's disease and Parkinson's disease. Asthma and some kinds of cancer undoubtedly belong in this cluster as well. Asthma has a large inflammatory component and pro-inflammatory triggers commonly provoke asthma attacks.

The initiation, promotion, and growth of many kinds of cancer are also fueled by excessive oxidative stress and a pro-inflammatory state.[20] [21] In order to limit the scope of this document, however, we will not include further discussion of asthma or cancer but hypothesize that their trends, too, would be favorably influenced by interventions designed to address the Western disease cluster.

We want to avoid being overly simplistic. Of course many factors are involved and we acknowledge areas of uncertainty, data gaps, and debate. Even within groups of individuals with the same disease, the origins of conditions will vary. In most of them, the disease will arise from a mixture of contributing causes. In some, genetic influences will play a more prominent role. In others, exposures to a toxic chemical or dietary pattern will be relatively more important. We emphasize that whatever causes individual cases of a disease is unlikely to be identical to what causes disease incidence and patterns in a population. However, from a medical, public health, and policy perspective, we think that it is useful to identify disease patterns and common origins where they exist. Then thoughtful interventions at many levels—individual, community, and societal—can help to prevent or mitigate several problems simultaneously. In a time of resource constraints, an overburdened healthcare system, and an approaching wave of age-related disease, preventing entire clusters of chronic debilitating illnesses should be a high priority.

Elder health is a key indicator of quality of life throughout the lifecycle, as well as an important issue in its own right.

Ours is a public health perspective with an emphasis on prevention. Our curiosity does not arise out of an anti-aging agenda with a primary goal of prolonging life but rather out of an interest in the quality of life of elders. Moreover, elder health is a key indicator of quality of life throughout the lifecycle, as well as an important issue in its own right. The narrative that emerges from the material that follows has decisive implications for public policy. These diseases are not just a matter of bad luck, individual responsibility, or personal choice. We argue that they are, in large measure, diseases of civilization and must, therefore, be addressed in that way. So, before turning to the diseases themselves, we first describe a number of relevant trends that have unfolded in the U.S. over the past 50–100 years. This lays out the context in which our discussion of diseases and disease patterns will begin.

Endnotes

1. U.S. Department of Health and Human Services, Administration on Aging. Available at: http://www.aoa.gov/prof/Statistics/statistics.aspx. Accessed June 2, 2008.
2. Bradley P, Walbeck E, Ghiloni J, editors. Proceedings of the aging Americans: impacts on ecology and environmental quality workshop; 2004 Aug 10-12. Research Triangle Park, NC. U.S. Environmental Protection Agency 2004. EPA/600/R-05/028.
3. Kinsella K, Velkoff V, US Census Bureau, Series P95/01-1, An Aging World: 2001. US Government printing office, Washington DC, 2001, pg 1.
4. Dr. Weil on Healthy Aging. Available at: http://www.drweilonhealthyaging.com/hya/ecs/a/home_ns.html. Accessed May 13, 2008.
5. Personal communication April 29, 2008.
6. U.S. EPA. Aging and toxic response: issues relevant to risk assessment. National Center for Environmental Assessment, Washington DC, 2005. EPA/600/P-03/00A. Available at: http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=156648. Accessed December 3, 2007.
7. U.S. Department of Health and Human Services, Administration on Aging. Available at: http://nihseniorhealth.gov/alzheimers-disease/defined/01.html. Accessed June 2, 2008.
8. Hebert LE, Scherr PA, Bienias JL, Bennett DA, Evans DA. Alzheimer disease in the US population: prevalence estimates using the 2000 census. Arch Neurol. 2003; Aug;60(8):1119-22.
9. World Health Organization. Neurological disorders: public health challenges. Geneva, Switzerland. February 2007. Available at: http://www.who.int/mental_health/neurology/neurodiso/en/index.html. Accessed March 20, 2007.
10. U.S. EPA. Op. cit.
11. Dorsey ER, Constantinescu R, Thompson JP, et al. Projected number of people with Parkinson disease in the most populous nations, 2005 through 2030. Neurology 2007;68: 384-386.
12. Alzheimer's Association. Available at: http://www.alz.org/AboutAD/statistics.asp. Accessed June 2, 2008.
13. Zhu CW, Scarmeas N, Torgan R, et al. Longitudinal study of the effects of patient characteristics on direct costs in Alzheimer disease. Neurology 2006;67: 998-1005.
14. Muir T, Zegarac M. Societal costs of exposure to toxic substances: economic and health costs of four case studies that are candidates for environmental causation. Environ Health Perspect. 2001; December;109(Suppl 6): 885-903.
15. Murman DL, Kuo SB, Powell MC, Colenda CC. The impact of Parkinsonism on costs of care in patients with AD and dementia with Lewy bodies. Neurology. 2003; Oct 14;61(7):944-9.
16. U.S. Department of Health and Human Services, Administration on Aging. Available at: http://www.aoa.gov/prof/notes/Docs/Alzheimer_Related_Dementia.pdf. Accessed June 2, 2008.
17. Mitchell SL, Teno JM, Miller SC, Mor V. A national study of the location of death for older persons with dementia. J Am Geriatr Soc. 2005; Feb;53(2):299-305. Erratum in: J Am Geriatr Soc. 2005 Apr;53(4):741.
18. World Health Organization. Neurological disorders: public health challenges. Geneva, Switzerland. February 2007. Page 34. Available at: http://www.who.int/mental_health/neurology/neurodiso/en/index.html Accessed December 3, 2007.
19. Misra A, Vikram N. Insulin resistance syndrome (metabolic syndrome) and obesity in Asian Indians: evidence and implications. Nutrition. 2004;20:482-49.
20. Harris R. Cyclooxygenase-2 (cox-2) and the inflammogenesis of cancer. Subcell Biochem. 2007;42:93-126.
21. Panayiotidis M. Ed: Oxidative stress and carcinogenesis special issue. Cancer Lett. 2008;266(1):1-98.

Chapter 2

The Changing Environment and Disease Patterns

The 20th century witnessed profound, unprecedented changes in the natural, built, and social environments. Countless new technologies introduced into diverse societies around the globe altered the ways we live. Dramatic changes in the patterns and distribution of human disease were inevitable.

Our purpose in this chapter is to note a few trends in the U.S. during the past century that are directly relevant to the health of an aging population. We wish to make explicit what may be obvious: compared to just a few decades ago, the circumstances out of which patterns of health or disease emerge have fundamentally changed.

"Every civilization creates the conditions for its own diseases."

René Dubos

Multi-dimensional Causal Webs of Disease

Many interdependent variables create a propensity for particular patterns of disease. These variables are woven together into multi-dimensional webs or networks, comprised of strands from the natural, built, and social environments, which in turn powerfully influence the practices and choices of our daily lives. Genetic changes in populations occur slowly and do not explain disease patterns that shift over years or decades. Environmental changes influence disease patterns much more rapidly and through many different pathways or mechanisms, some of which are discussed in subsequent chapters of this report.

Scientists long ago acquired the habit of taking complex systems apart in order to study individual components. That approach has been enormously fruitful in many respects but has limited value for predicting novel, emergent properties of complex, interactive systems. To be more fully understood, causal webs of disease must ultimately be considered not only as a collection of individual strands but also in their integrated complexity.

The plum blossom is a symbol of longevity in Asian cultures.

To be more fully understood, causal webs of disease must ultimately be considered not only as a collection of individual strands but also in their integrated complexity.

Today's disease patterns are quite different from those of a century ago. Changes in the built and social environments, as well as public health and medical advances, have contributed to longer life expectancies. But independent of longevity, some of these changes have also profoundly influenced the nature of diseases throughout the lifespan. Obviously, people must ultimately die of something, but today's disease patterns are not an inevitable price that must be paid for longer life. Rather, many of today's diseases, including those that disproportionately affect the quality of life in an aging population, could be delayed or prevented.

The Epidemiologic Transition

The growth of cities throughout the 1800s created conditions at the beginning of the 20th century in which infectious diseases flourished.[1] Life expectancy at birth in the U.S. in 1900 was 47 years. Infant mortality from infectious disease was common, and pneumonia, tuberculosis, and influenza were leading causes of death in adulthood. Improved sanitation, housing, standards of living, vaccines, antibiotics, and other medical interventions led to dramatic declines in infectious disease morbidity and mortality. Biomedical research and education made important contributions to shifting disease patterns and the outcomes of many diseases, but most historians give public health interventions credit for the largest impacts. By the end of the 20th century, life expectancy at birth had reached 77 years, although significant disparities remained among races and classes.

This increase in life expectancy was accompanied by an "epidemiologic transition" to new patterns and distribution of disease, from high mortality among infants and children, along with episodic famine and infectious epidemics affecting all age groups, to more chronic, degenerative diseases.[2] Among children in the U.S. in the latter part of the 20th century, premature birth, injuries, asthma, neurodevelopmental disorders, birth defects, cancer, and obesity became principal causes of morbidity and mortality. In adults, diabetes, obesity, cardiovascular disease, cancer, respiratory diseases, mental illness, and neurodegenerative diseases became major concerns. Similar transitions are underway in other parts of the world where cardiovascular disease, cancer, mental health disorders, obesity, and diabetes are becoming increasingly common. In developing countries, however, infectious diseases continue to be a major cause of morbidity and mortality.

An Overview of 20th Century Environmental Change

During the 20th century, human activity began to dominate the world's ecosystems in unprecedented ways. Rapidly developing new technologies exponentially leveraged human power and ingenuity, but technological advancement was on a steep learning curve and unintended consequences were common. Development and use of the atomic bomb in the 1940s put humanity on notice that we are capable of destroying planetary life as we know it.

In the late 1960s Rachel Carson warned that rapid development and deployment of industrial chemicals in agriculture threatened the entire food web and health of ecological systems. Photos from space travel cemented in people's minds the realization that we live on a small, hospitable planet in a forbidding universe. The discovery of a hole in the stratospheric ozone layer related to using chlorofluorocarbon refrigerants shocked many people into understanding that we were capable of destroying planetary control mechanisms before we even knew that they existed. We discovered a kind of mistake born out of profound ignorance—not even knowing what question to ask when considering the impact of a new technology. Ethical constraints on technological advancements became an increasingly urgent topic of public debate.

In 2005 the United Nations released the Millennium Assessment, the most comprehensive survey of the status of global ecosystems ever attempted. It began by reminding us how dependent we are on ecosystems for services such as climate control, air and water cleansing, soil fertility, pollination, and the like. It told us that in the past 50 years, humans have changed ecosystems more rapidly and extensively than in any comparable period in human history. During that time, global population has increased from 2.5 to over 6 billion people. Planetary systems are being stressed in novel ways and are increasingly unstable. Many are approaching thresholds beyond which lie little prospect for returning to previous operating conditions.

In summary, human activity has altered virtually every aspect of ecological systems throughout the world in unprecedented ways. Climate instability with periods of extreme heat, degraded soil, air, and water quality, and loss of biodiversity and ecosystem services

United Nations Millennium Assessment: Highlights of Key Findings[3]

IN 2005, THE UNITED NATIONS and collaborating partners released the Millennium Assessment, the largest evaluation of the health of the earth's ecosystems ever undertaken. Over 1300 experts from 95 countries prepared the extensively peer-reviewed report.

Among the key findings:

- Between one-third and one-half of the land surface of the earth has been transformed by human activity.
- The changes have contributed to net gains in human well-being and economic development but these gains are not evenly distributed. They have been achieved at growing costs in the form of the degradation of many ecosystem services and the exacerbation of poverty for many groups of people.
- UN researchers estimate that there were at least 921 million slum dwellers in 2001 and more than one billion in 2005, with slum populations growing by 25 million per year.
- Growing pressures from over-harvesting, climate change, invasive species, and nutrient loading push ecosystems toward thresholds that they might otherwise not encounter.
- Approximately 60 percent (15 out of 24) of the ecosystem services evaluated in this assessment are being degraded or used unsustainably.
- The degradation of ecosystem services often causes significant harm to human well-being and represents a loss of a natural asset or wealth of a country.
- Changes in ecosystems increase the likelihood of nonlinear changes (including accelerating, abrupt, and potentially irreversible changes), with important consequences for human well-being.
- Loss of species and genetic diversity decreases the resilience of ecosystems.
- The climate is warming with more extreme events such as flooding, hurricanes, and drought.
- Carbon is in positive balance; carbon is released into atmosphere and oceans; CO_2 concentration in the atmosphere has increased by about 30 percent since the beginning of the industrial revolution and is now at 380 ppm—near a critical tipping point.
- More atmospheric nitrogen is fixed by humanity than by all natural terrestrial sources combined. Fertilizer production and fossil fuel combustion are largely responsible. Nitrogen dioxide is a greenhouse gas and ozone precursor.
- Greenhouse gas effects cause melting of glaciers and permafrost and release of methane from peat bogs, resulting in more warming.

- Twenty-five percent of mammals and thirty percent of amphibians are threatened with extinction.
- One-quarter of the bird species on earth have been driven to extinction; twelve percent of those left are threatened with extinction.
- Novel synthetic industrial chemicals contaminate the world's ecosystems, humans, and other species.
- The food supply of humans and other creatures is contaminated at levels of concern.

Food

- Food production has more than doubled since 1960.
- Food production per capita has grown; for many people, food prices fell and were relatively low at the time of the Millennium Assessment. This is now changing with the increasing costs of fossil fuels and pressure on agricultural land to produce biomass for fuel production.
- Forty percent of the earth's land is in agriculture. Clearing land results in loss of valuable ecosystem services from forests and wetlands.
- Industrialization of agriculture leads to change in nutritional composition of food.
- Air, water, and soil are contaminated with pesticides, hormones, growth promoters, antibiotics, nitrates, and manure effluents.
- Rural communities have undergone social disruption.
- Approximately two-thirds of major marine fisheries are fully exploited, overexploited, or depleted.
- An estimated ninety percent of the total weight of the ocean's large predators—tuna, swordfish, and sharks—has disappeared in recent years.

Water

- One billion people lack access to fresh water.
- More than one-half of all accessible fresh water is used by humans; much of it is contaminated.
- Digestive-tract diseases arising from poor sanitation and the pollution of drinking water are the leading cause of death in the world, affecting mainly infants and small children.
- Oceans have been acidified by CO_2 released by fossil fuel combustion; the marine food web is threatened.
- Nitrates contaminate groundwater and surface water; nitrates, along with phosphorous, cause eutrophication (excessive nutrient loading and oxygen depletion) of water systems.

Virtually all people and wildlife are regularly exposed to a complex mixture of industrial chemicals that did not previously exist in human history.

collectively increase the risks of a number of diseases or conditions in all people. Economic inequities and disparities in healthcare access put poor, unempowered people at greater risk from both chronic illness and environmental threats. Within this context, the elderly population is often particularly vulnerable because of normal functional decline in some adaptive regulatory mechanisms as well as underlying chronic disease conditions.

The Chemical, Built, and Social Environments

Where and how we live, eat, work, play, and socialize profoundly influence our physical and mental health. During the 20th century, as infectious diseases were better controlled through public health measures and medical advances, new disease patterns developed related to changes in activities, diet, work, housing, exposure to environmental contaminants, and social organization.[a 4]

Rapid industrialization and nearly ubiquitous contamination of air, soil, and water with hazardous waste, byproducts of resource extraction, fossil fuel combustion, and synthetic chemicals continued in the U.S. during the 20th century. Pesticides and other industrial chemicals, some of them persistent and bioaccumulative (concentrating themselves in living organisms), contaminate people, wildlife, and the general environment.

The Pervasive Spread of Synthetic Chemicals

From its pre–World War II infancy the chemical industry grew to account for about 2 percent of the U.S. GDP.[5] Now the U.S. imports or produces approximately 42 billion pounds of chemicals daily.[6] Global chemical production is expected to double every 25 years. Over 77,000 hazardous waste sites in the U.S. are an enduring legacy of the mismanagement of industrial chemicals over many decades. Synthetic chemicals contaminate every ecosystem in the world. Virtually all people and wildlife are regularly exposed to a complex

[a] Rural-to-urban migration, the industrialization of agriculture, changes in the scope and scale of resource extraction, materials manufacture, construction, transportation, communication, and birth of the military-industrial, medical-industrial, and academic-industrial complexes are among the most dramatic shifts.

mixture of industrial chemicals that did not previously exist in human history.[7] Babies are now born having already been exposed to industrial chemicals in the womb.[8]

Most industrial chemicals in the workplace and in consumer products have not undergone even basic toxicity screening.[9] Only a few of 200 chemicals that are neurotoxic in humans have been evaluated for their impacts on the developing brains of children or aging brains of adults.[10] Data that do exist show that exposures to environmental chemicals can increase the risk of many diseases and conditions relevant to an aging population, including neurodegenerative disorders, cardiovascular disease, hypertension, and diabetes.[11]

Commonly used sewage treatment technologies do not remove many pharmaceuticals from the waste stream before discharge into the environment.

When restrictions on hazardous chemical production, use, and disposal have been successful, public health has benefited. For example, a ban on the use of tetraethyl lead in gasoline resulted in marked declines in average blood lead levels in the U.S. Yet many children continue to be exposed to unsafe levels, and adults carry the lead legacy of the past imbedded within them. As we will show, early life exposures to lead are likely to increase the risk of Alzheimer's disease and Parkinson's disease later in life. Unfortunately, restrictions on hazardous chemicals have been extremely limited, and ongoing exposures continue to pose health risks.

Racial differences in the location of hazardous waste sites and exposures to hazardous environmental substances have created unequal health risks for low income groups and ethnic and racial-minority communities.[12 13] Known as environmental injustice, this trend is one among many factors that are likely to contribute to racial health disparities.

The Clean Air Act and Clean Water Act of the 1970s led to improvements in some aspects of air and water quality.[14] Nonetheless, hazardous levels of particulate air pollution, ozone, agricultural and industrial chemicals, and greenhouse gases continue to cause disease in the U.S. and globally. The ozone 8-hour standard was exceeded for nearly half of elderly adults in 2002, and this proportion has been increasing since the year 2000.[15] Particulate air pollution is directly associated with increases in markers of inflammation in both young and elderly individuals.[16 17] People with underlying diabetes, obesity, and hypertension appear to be particularly susceptible. Air pollution is a commonly encountered risk factor for neurodegenerative diseases.[18] A large body of evidence also links particulate air pollution to premature deaths from cardiovascular disease.[19] Later

People who live in neighborhoods that lack social cohesion, sidewalks, or safety limit their exercise and have an increased risk of depression and possibly obesity.

chapters of this report explain what happens at the cellular level when the body encounters pollutants and other stressors.

Medical pharmaceuticals have their own environmental impacts. A number of prescription and non-prescription drugs or their metabolic byproducts, including antibiotics, anti-inflammatories, antidepressants, cholesterol-lowering agents, and hormones are present in surface waters and drinking water sources around the country.[20 21] Commonly used sewage treatment technologies do not remove many pharmaceuticals from the waste stream before discharge into the environment. Concentrations of detected drugs are low, but the health risks resulting from exposure to the complex mixture in people and wildlife are uncertain.

The Workplace

Workplace conditions and hazardous exposures have always been major determinants of health risks among workers and in communities where hazardous substances are released. Occupational medicine was slow to develop in the U.S. because of opposition from corporations, cheap immigrant labor, and lack of union organizing.[22] Alice Hamilton was the first American physician to devote her career to occupational medicine. She studied and described effects of workplace exposures in her classic *Industrial Poisons in the United States* (1925).

Union organizing along with increased government oversight helped to improve working conditions in many ways in the 20th century, but over the past 40 years in the U.S., union membership and influence has steadily declined. Many occupations continue to expose workers to elevated risks of injury and disease. Occupational diseases and injuries have probably always been under-recognized and under-reported, and estimates of the degree to which workplace conditions contribute to disease patterns vary widely. Multifactorial diseases such as cancer, heart disease, and neurodegenerative disorders are

probably always under-represented. One estimate in the 1990s concluded that direct and indirect costs of occupational diseases and injuries in the U.S. totaled $171 billion annually. This estimate is almost certain to be low.[23]

The Indoor Environment

Many people now spend more than 90 percent of their time in buildings, and the indoor environment has recently received much-needed attention. New construction techniques and materials introduced in the latter half of the 20th century, along with the widespread use of central heating and air-conditioning, dramatically changed the indoor environment in homes, commercial, and public buildings. In many buildings, indoor air is contaminated with a complex mixture of chemicals from many sources, including emissions from building materials and other consumer products, fuel combustion, and mold. Studies show that indoor air pollution often exceeds outdoor levels.[24 25] Disease risks related to the indoor environment vary with levels of specific contaminants but can include asthma, bronchitis, cancer, and reproductive, developmental, and neurological disorders.

Poverty rates among older people living alone are higher than those of people living with others.

Activity and Isolation

Regular exercise has undeniable health benefits. Exercise levels are in large measure a matter of individual choice but are also influenced by competing time demands and community features. People who live in neighborhoods that lack social cohesion, sidewalks, or safety limit their exercise and have an increased risk of depression and possibly obesity.[26 27 28 29]

Not surprisingly, higher "walkability" ratings of neighborhoods are associated with significantly more walking.[30 31] Suburban sprawl has contributed to a marked decline in exercise levels in children and adults who are increasingly dependent on cars to get where they want to go.

Sprawl, television, computers, and internet access also contribute to increasing social isolation.[32] We have largely shifted from being a communal to a more individualistic society and have created a world where we often live among strangers.[33]

Increasing numbers of elders are living alone, although this varies according to gender and ethnicity. Over the past 30 years, the proportion of elderly people over 75 years of age living alone has increased for men (from 19.1 to 23.1 percent) and women (from 37 to 49.9 percent).[34] Women over 65 are more than twice as likely as

men to live alone (40 percent vs. 19 percent), although the numbers are lower among Asian women (20 percent) and Hispanic women (26 percent) and Asian men (8 percent) and Hispanic men (15 percent). Twenty-nine percent of black men over 65 live alone.

Although the number has declined in recent years, about 1.5 million people live in nursing homes, and an unknown number live in assisted living facilities.[35]

Economic Status

Poverty rates among older people living alone are higher than those of people living with others.[36] In the U.S., the growing income gap between the rich and poor is one of the most significant recent trends with striking medical and public health implications.[37] Before World War II large income disparities were common, but in the post-war years, that gap began to narrow and a large middle class emerged. Since the late 1960s, however, that gap has steadily grown so that today, the disparities resemble those of the 1930s.[38] In 1970, according to the Census Bureau, the bottom fifth of families received 5.4 percent of total national income while the richest fifth received 40.9 percent of the total. Twenty-five years later the bottom fifth's share had fallen to 4.4 percent while the top fifth had increased to 46.5 percent. By 2001 the top 1 percent of households held 33.4 percent of all net worth in the U.S..

While most people are aging, their incomes are declining. The number of older people living in poverty has dramatically declined over the past half-century, from 35 percent in 1959 to 9 percent in 2006. However, even now, this increases to 35 percent when those living on a low income are added. Older non-Hispanic whites are much less likely than their Hispanic and black counterparts to be living in poverty, about 7 percent compared to 19 percent and 23 percent respectively. In all groups, older women are poorer than older men. For all Americans over 65 in 2006, Social Security constituted 37 percent of their aggregate income, but it is 80 percent of total income for those in the lowest quintile.[39] [40] Collectively, social and economic conditions are powerful predictors of stress levels, health status, disease risk, and life expectancy.[41]

Nutrition

During the 20th century dramatic changes in food technologies altered food availability and dietary patterns. Commercial canning, freezing, and packaging techniques advanced. Home refrigeration lengthened storage life and many foods became more widely available, including meat and poultry. In the middle decades of the century, in response to increased understanding of the role of specific nutrient deficiencies in human disease, some foods were fortified with vitamins and minerals.

Shaped by the industrial model in other sectors, agricultural practices underwent profound changes during the 20th century. New plant and animal hybrids; increased reliance on mechanization; high inputs of petrochemical fertilizers, pesticides, and fuels; and the involvement of large corporations in all phases of food production and marketing progressively industrialized food production in the U.S. and other countries. Yields increased, many foods became routinely available to larger numbers of people, and food prices declined, particularly as a percentage of income.

More and more acreage was shifted into large commodity crops of corn, soybeans, and wheat. Beef, pork, and poultry production became more concentrated in large confined feedlots where animals are more rapidly grown and brought to market with grain-based diets, often supplemented with routine use of growth-promoting antibiotics and hormones.

This approach came with costs that have never adequately been reflected in the price of food. Industrial agriculture forever changed the rural landscape and rural communities. Topsoil loss; pollution of air and water with agricultural chemicals; eutrophication of lakes, rivers, and coastal waters; loss of habitat and biodiversity; and economic hardship in farming communities are the legacy of this agricultural revolution.

Changes in food production systems also brought change in the composition of food. The meat of animals raised in confined feedlots has significantly higher ratios of omega-6 to omega-3 fatty acids than do pasture-fed or free-range counterparts.[42] Industrial-style production of poultry has had a similar impact. A 2006 report of 43 garden crops, based on USDA data, noted a significant decline in protein, calcium, iron, phosphorus, riboflavin and ascorbic acid over the past 50 years, with no decline in vitamin A, thiamin, niacin, fat,

Topsoil loss; pollution of air and water with agricultural chemicals; eutrophication of lakes, rivers, and coastal waters; loss of habitat and biodiversity; and economic hardship in farming communities are the legacy of this agricultural revolution.

Table 1: Foods available in U.S. food supply (per person per year), by major food group for selected years.

Year	1909	1945	1975	1999
		(Lbs. per person)		
Meat	228	257	261	298
Meat, poultry, and fish	176	188	207	245
Red meat	148	153	148	134
Poultry	17	26	47	95
Fish	11	10	12	15
Milk and milk products	345	552	453	502
Whole milk	229	344	181	72
Lowfat milks	65	40	60	131
Cheese	4	9	19	32
Other dairy	29	130	129	138
Vegetables and vegetable juices	414	400	279	302
White potatoes	188	120	82	87
Deep-yellow and dark-green vegetables	35	46	25	36
Other vegetables	145	174	127	134
Tomatoes	46	61	44	45
Fruit and fruit juices	173	207	189	232
Citrus fruits	16	71	77	78
Noncitrus fruits	157	135	112	153
Grain products	300	204	139	200
Sugars and sweeteners	84	92	118	158
Fats and oils	41	42	56	73
Butter	18	11	5	5
Margarine	1	4	11	8
Shortening	8	9	17	22
Lard and beef tallow	13	12	3	6
Salad, cooking, and other oils	2	6	20	32

or carbohydrate.[43] Highly processed food that is calorie rich and nutrient poor became widely available and is heavily promoted, especially to children.[44]

From 1970 to 2003, the average caloric intake per person per day increased from 2,234 to 2,757, after adjusting for waste and spoilage.[45] Table 1 shows foods available in the U.S. food supply (per person annually), by major food group over a longer time frame.[46]

Trans fats are now believed to be major contributors to heart disease risk, and food producers are under increasing pressure to eliminate them.

Several trends are noteworthy:

- Grain product availability was considerably lower in 1999 than in 1909, although it increased after 1975.
- The use of sugars and sweeteners has increased by over 30 percent in the past 25 years. Corn sweeteners surpassed the use of sugar in the 1980s and per-capita consumption of corn syrup increased to 79 pounds in 2003, up 400 percent from 1970.[47]
- Deep yellow and dark green vegetable consumption stayed relatively constant. (These are major sources of dietary antioxidants.) White potato consumption declined dramatically during the first half of the 20th century but has increased in recent years, primarily because of the popularity of frozen and French fried potatoes.
- The consumption of fats and oils remained relatively constant through the first half of the 20th century but then began to increase dramatically. By 1999 annual per-person consumption of fats and oils had increased by 78 percent.

Various forces, including dramatic increases in fried foods in the fast-food industry, raised fat consumption.[48] During the 20th century, the incidence of heart disease rapidly increased, and in the last 50 years, the role of dietary fats has received much attention.

In the 1960s an ongoing landmark epidemiologic study (the Framingham study) established a link between serum cholesterol levels and heart disease risk. Saturated fats were thought to play a

dominant role, and many nutritionists recommended a shift from butter and lard to vegetable oils and margarine containing polyunsaturated fatty acids (PUFAs).

For some time, important differences among PUFAs were not understood. PUFAs are much more susceptible to oxidation than saturated fatty acids, making them more likely to turn rancid. Among the PUFAs, however, linoleic acid (an omega-6 fatty acid) is much less susceptible to oxidative damage than linolenic acid (an omega-3 fatty acid). Thus, linolenic acid is much less likely to be used in processed food. Although it is true that many polyunsaturated oils lower serum cholesterol and do not contain cholesterol themselves, it was not realized until more recently that some forms of linoleic acid, the most prevalent fatty acid in many vegetable oils, can contribute to inflammation, particularly when intake of omega-3 fatty acids is not adequate.[49] [50]

The shift to unsaturated cooking oils brought yet another unintended consequence. Early in the 20th century, the process of hydrogenating vegetable oils came into widespread use when the resulting semi-solid products were noted to extend the shelf life and, according to some people, improve the taste of baked goods. Later, partially hydrogenated oils were also promoted because they lacked saturated fat. As was later learned, however, the process of partially hydrogenating oils also created trans fats, a particularly unhealthy form of unsaturated fatty acids. Trans fats not only lower levels of good cholesterol and raise bad cholesterol but they also sharply increase markers of inflammation.[51] Trans fats are now believed to be major contributors to heart disease risk, and food producers are under increasing pressure to eliminate them.

As we will later discuss in more detail, today's diet containing trans and saturated fats and inadequate levels of omega-6s and omega-3s is virtually certain to directly contribute to risks of cancer, heart disease, arthritis, obesity, cognitive decline, and in all likelihood, numerous other diseases.[52]

Given their economic conditions, older Americans often have less choice about where they live, what they eat and drink, and how active they can be. Consequently, their nutrition may suffer. Indeed, according to the Healthy Eating Index, the diets of over 75 percent of older Americans need improvement. This rises to over 90 percent for those living below the poverty level.[53]

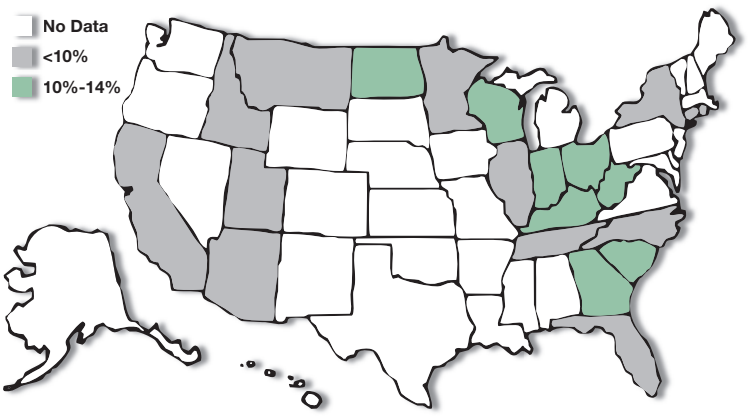
Select Disease Trends in the 20th Century

Of the new disease patterns that mark the 20th century we will highlight obesity, diabetes, cardiovascular disease, and hypertension because of their relevance to neurodegenerative conditions later in life. Trends in cancer incidence are available from the National Cancer Institute.[54] Trends in Alzheimer's disease and Parkinson's disease are discussed in later chapters.

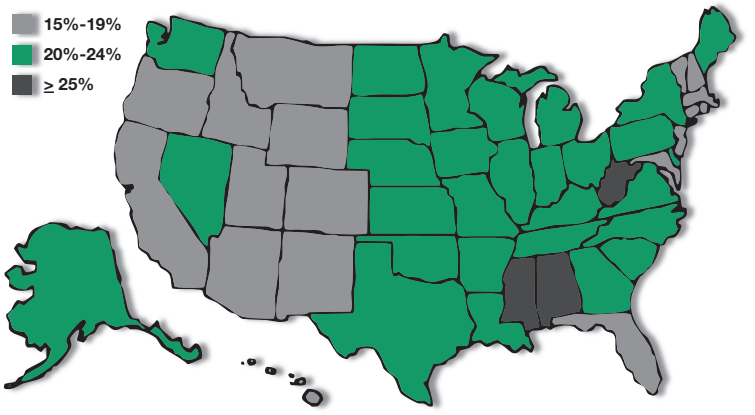
Overweight and Obesity

By themselves, overweight and obesity are not necessarily diseases, but they increase the risk of hypertension, type 2 diabetes, coronary heart disease, abnormal lipid profile, stroke, gall bladder disease, some cancers (endometrial, breast, colon), sleep apnea, osteoarthritis, and Alzheimer's disease.[55] In many people, obesity is also associated with increased levels of markers of inflammation and oxidative stress. For these reasons, trends in these conditions are highly relevant to disease patterns in human populations. As we can see from the accompanying figures, the prevalence of obesity among adults in the U.S. has increased dramatically in recent years.[b]

Obesity Trends Among U.S. Adults 1985

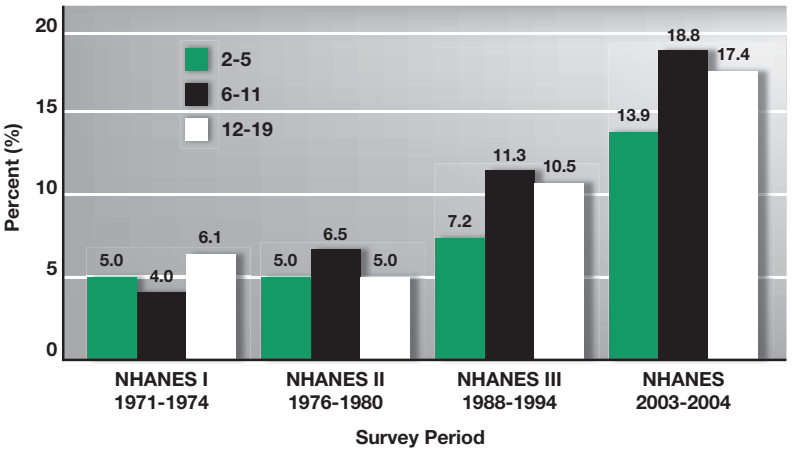


Obesity Trends Among U.S. Adults 2002



[b] *For adults, overweight and obesity ranges are determined by using weight and height to calculate a number called the "body mass index" (BMI). An adult who has a BMI between 25 and 29.9 is considered overweight. An adult who has a BMI of 30 or higher is considered obese. A BMI calculator is available at: http://www.cdc.gov/nccdphp/dnpa/bmi/index.htm. Map trends source: Behavioral Risk Factor Surveillance System, CDC.*

Prevalence of Overweight* Among U.S. Children and Adolescents (Aged 2 –19 Years) National Health and Nutrition Examination Surveys



*Sex-and age-specific BMI > 95th percentile based on the CDC growth charts.

Source: Centers for Disease Control and Prevention. Overweight and obesity.Available at: "http://www.cdc.gov/nccdphp/dnpa/obesity/" Accessed 5/30/08

Childhood Overweight and Obesity

Overweight is also a serious health concern for children and adolescents. Data from two NHANES surveys (1976–1980 and 2003–2004) show that the prevalence of overweight is increasing: for children aged 2–5 years, prevalence increased from 5.0 percent to 13.9 percent; for those aged 6–11 years, prevalence increased from 6.5 percent to 18.8 percent; and for those aged 12–19 years, prevalence increased from 5.0 percent to 17.4 percent.[56]

Healthy People 2010 identified overweight and obesity as one of ten leading health indicators and called for a reduction in the proportion of children and adolescents who are overweight or obese.[57] A recent report concludes that the upward trend in childhood obesity may have leveled off.[58]

Diabetes

The accompanying figures, from the Centers for Disease Control and Prevention, show the extent to which diabetes has become more prevalent in all age groups in the U.S. in the past twenty-five years.[59]

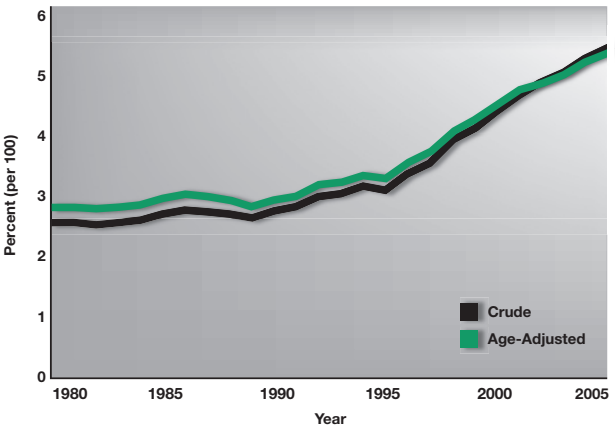
The best available evidence suggests that childhood type 1 diabetes showed a stable and relatively low incidence over the first half of the 20th century, followed by a clear increase that began at some time around or soon after the middle of the century, with an incidence now of three or four in a thousand.[60] In recent years, type 2

diabetes, previously a phenomenon of later life and frequently associated with obesity, has become a significant and growing problem even among children.[61]

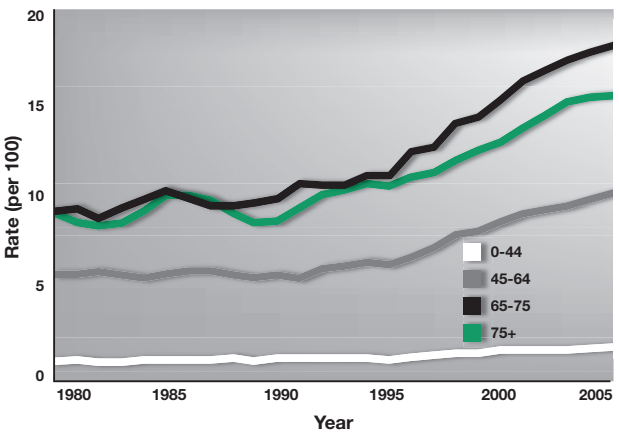
Cardiovascular Disease

Cardiovascular disease and its associated risk factors are increasingly recognized as risk factors for both Alzheimer's disease and vascular dementia. A sharp upturn in the incidence of cardiovascular disease during the middle of the 20th century led to considerable research into its origins and measures to prevent it. Declines in death from cardiovascular disease during the past 25 years are due to a combination of factors including early detection, smoking reduction (the first surgeon general's report on smoking and health was issued in 1964), blood pressure control, decrease in blood cholesterol levels through dietary changes, and improvements in medical care, including emergency management and pharmaceutical interventions.[62] According to one analysis, about half of the reduction in cardiovascular mortality can be explained by reduction in risk factors, and the other half by pharmaceutical and other therapeutic interventions.[63] Heart disease, however, remains the leading cause of death in men and women in the U.S.[64]

Percent of people with diabetes:



Age adjusted prevalence of diabetes:



Source: Center for Disease Control and Prevention. Diabetes data and trends. Available at: "http://apps.nccd.cdc.gov/DDTSTRS/default.aspx" Accessed 5/30/08

Hypertension

According to the Centers for Disease Control, the prevalence of hypertension, defined as elevated blood pressure or taking antihypertensive medication, increases with age. In 2001–2004, 30 percent of men and 33 percent of women age 45–54 years had hypertension. This increases to 69 percent of men and 82 percent of women age 75 years and over.[65] Although data gaps make it difficult to determine changes in prevalence over many decades, evidence is sufficient to conclude that age-adjusted hypertension increased in the U.S. population during the years 1988–2000.[66]

While many features of today's world promote health and enjoyment, some also increase the risk of chronic, degenerative diseases later in life.

Conclusion

We have briefly described significant changes in many aspects of the natural, built, and social environments that have occurred over the past 50–100 years. Public health and medical advances have contributed to increased longevity. The epidemiologic transition to today's disease patterns has occurred within that context.

In this broad overview of macro-level variables, we begin to see some of the drivers of health and disease patterns. While many features of today's world promote health and enjoyment, some also increase the risk of chronic, degenerative diseases later in life—widespread exposure to toxic chemicals and other environmental contaminants, increasing social stress and isolation, inactivity, and diets heavily influenced by an agricultural system that is dependent on high inputs of fuels, chemicals, and fertilizers and geared more to shelf-life and transportability than to nutrient balance.

We will soon look more closely at the details of how some of these pose threats to healthy brain aging and contribute to other associated chronic illnesses. In preparation for that we turn first to a short primer on brain function.

Endnotes

1. Frumkin H, Frank L, Jackson R. Urban Sprawl and Public Health: Designing, Planning, and Building for Healthy Communities. Washington, DC: Island Press; 2004.
2. Omran A. The epidemiologic transition: a theory of the epidemiology of population change. Milbank Quarterly. 1971;49:509-538. Available at http://www.milbank.org/quarterly/830418omran.pdf Accessed Aug, 2007.
3. The Millennium Ecosystem Assessment. Available at: http://www.millenniumassessment.org/en/Index.aspx Accessed July 5, 2008.
4. Kenneth Johnson. Demographic trends in rural and small town America. University of New Hampshire, 2006. Available at: http://www.luc.edu/sociology/pdfs/Demographics_complete_file.pdf . Accessed August 13, 2007.
5. Lenz A, Lafrance J. Meeting the challenge: U.S. industry faces the 21st century. The chemical industry. US Dept of Commerce, 1996. Available at: http://www.technology.gov/Reports/chemicals/chemical.pdf. Accessed May 29, 2008.
6. Wilson M. Green chemistry in California: a framework for leadership in chemicals policy and innovation. California Policy Research Center. University of California, 2006. Available at: http://coeh.berkeley.edu/docs/news/06_wilson_policy.pdf Accessed May 29, 2008.
7. National Report on Human Exposure to Environmental Chemicals. Centers for Disease Control. Dept of HHS. Available at: http://www.cdc.gov/exposurereport/results_02.htm. Accessed May 28, 2008.
8. Environmental Working Group. Body burden: the pollution in newborns. 2005. Available at: http://archive.ewg.org/reports/bodyburden2/ Accessed May 28, 2008.
9. US Government Accounting Office. Chemical regulation: actions are needed to improve the effectiveness of EPA's chemical review program. GAO-06-1032T. 2006. Available at: http://www.gao.gov/new.items/d061032t.pdf Accessed June 1, 2008.
10. Grandjean P, Landrigan P. Developmental neurotoxicity of industrial chemicals. Lancet. 2006;368(9553):2167-78.
11. Collaborative on Health and Environment Toxicant and Disease Database. Available at: http://database.healthandenvironment.org/ . Accessed May 30, 2008.
12. Bullard R. Dumping in Dixie: Race, Class, and Environmental Quality. Third edition. Boulder CO: Westview Press; 2000.
13. Montague T. The dangers of being poor and nonwhite. Rachel's Democracy and Health News #848. Available at: http://www.rachel.org/en/node/6405. Accessed May 30, 2008.
14. US EPA. National air pollutant emission trends 1900-1998. US EPA Document Number 454/R-00-002, March 2000. Available at: http://www.epa.gov/ttn/chief/trends/trends98/. Accessed October 2, 2007.
15. US EPA. Aging and toxic response: issues relevant to risk assessment. National Center for Environmental Assessment, Washington DC, 2005; EPA/600/P-03/00A. Available at: http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=156648. Accessed December 3, 2007.
16. Calderón-Garcidueñas L, Solt AC, Henríquez-Roldán C. et al. Long-term air pollution exposure is associated with neuroinflammation, an altered innate immune response, disruption of the blood-brain barrier, ultrafine particulate deposition, and accumulation of amyloid beta-42 and alpha-synuclein in children and young adults. Toxicol Pathol 2008; 36(2): 289-310.
17. Dubowsky S, Suh H, Schwartz J, CoullB, Gold D. Diabetes, obesity, and hypertension may enhance associations between air pollution and markers of systemic inflammation. Environ Health Perspect. 2006;114(7):992-998.
18. Calderón-Garcidueñas L, Reed W, Maronpot R, et al. Brain inflammation and Alzheimer's-like pathology in individuals exposed to severe air pollution. Toxicol Pathol. 2004;32(6):650-658.
19. Reviewed in: Pope C, Dockery D. Health effects of fine particulate air pollution: lines that connect. J Air Waste Manag Assoc. 2006;56(6)709-742.
20. Daughton, C.G. Pharmaceuticals in the environment: sources and their management. In: M. Petrovic and D. Barcelo, eds. Analysis, Fate and Removal of Pharmaceuticals in the Water Cycle, Wilson & Wilson's Comprehensive Analytical Chemistry series, Volume 50. Elsevier Science; 2007:1-58. Non-copyrighted web version. Available at: http://www.epa.gov/esd/bios/daughton/Chap1_Petrovic&Barcelo.pdf Accessed May 30, 2008.
21. US EPA. Pharmaceuticals and Personal Care Products. Available at: http://epa.gov/ppcp/faq.html#Inwhattypes. Accessed May 31, 2008.
22. Rom W. The discipline of environmental and occupational medicine. In: Rom W, ed: Environmental and Occupational Medicine. Second Ed. Boston, MA: Little, Brown; 1992.
23. Leigh J, Markowitz S, Fahs M, Shin C, Landrigan P. Occupational injury and illness in the United States: estimates of costs, morbidity, and mortality. Arch Intern Med. 1997;157(14):1557-1568.
24. US EPA's 2007 Report on the Environment: Highlights of National Trends. Peer review and public comment draft, August 2007. Available at: http://www.epa.gov/indicators/. Accessed December 3, 2007.
25. US EPA. Fact Sheet "Age Healthier Breathe Easier" June, 2007. Available at: http://www.epa.gov/aging/resources/factsheets/ahbe_english_2007_06.pdf. Accessed December 3, 2007.
26. Molnar BE, Gortmaker SL, Bull FC, Buka SL. Unsafe to play? Neighborhood disorder and lack of safety predict reduced physical activity among urban children and adolescents. Am J Health Promot. 2004.18(5):378-86.
27. Fisher KJ Li F, Michael Y, Cleveland M. et al. Neighborhood-level influences on physical activity. J Aging Phys Act. Jan 2004;12(1):45-63.
28. Berke EM, Gottlieb LM, Moudon A, Larson EB. Protective association between neighborhood walkability and depression in older men. Journal of the American Geriatrics Society 55 (4),526–533. doi:10.1111/j.1532-5415.2007.01108.x
29. Hybels CF et al. Sociodemographic characteristics of the neighborhood and depressive symptoms in older adults: using multilevel modeling in geriatric psychiatry. Am J Geriatr Psychiatry. 2006;14:498-506.
30. Berke EM, Koepsell TD, Moudon AV, Hoskins RE, Larson EB. Association of the built environment with physical activity and obesity in older persons. Am J Public Health. Mar 2007;97(3):486-92. Epub 2007 Jan 31.
31. King WC, Belle SH, Brach JS, Simkin-Silverman LR, Soska T, Kriska AM. Objective measures of neighborhood environment and physical activity in older women. Am J Prev Med. Jun 2005;28(5):461-9.
32. Putnam R.D. Bowling Alone: The Collapse and Revival of American Community. New York: Simon & Schuster; 2000:210

33. Pipher M. In Another Country. Navigating the Emotional Terrain of Our Elders. New York: Penguin Putnam Inc.; 1999:69.
34. Federal Interagency Forum on Age-Related Statistics. Older Americans Update 2008: Key Indicators of Well-being. Washington, DC. US Government Printing Office. March 2008.
35. National Center for Health Statistics. Available at: http://www.cdc.gov/nchs/data/nnhsd/Estimates/Estimates_Demographics_Tables.pdf#Table01 Accessed July 22, 2008.
36. The American Geriatric Society. Trends in the Elderly Population. March 2005. Available at: http://www.healthinaging.org/aginginthe know/chapters_ch_trial.asp?ch=2#Living percent20Arrangements. Accessed August 13, 2007.
37. Gudrais E. Unequal America. Harvard Magazine. July-Aug, 2008. Available at: http://harvardmagazine.com/2008/07/unequal-america.html Accessed July 5, 2008.
38. US Census Bureau. US Dept of Commerce. The changing shape of the nation's income distribution. June 2000. Available at: http://www.census.gov/prod/2000pubs/p60-204.pdf. Accessed May 30, 2008.
39. Association on Aging. A Profile of Older Americans:2007. Available at: http://www.aoa.gov/PROF/Statistics/profile/2007/2.asp. Accessed June 1, 2008
40. Federal Interagency Forum on Aging-Related Statistics. Older Americans Update 2008: Key Indicators of Well-being. Washington, DC. US Government Printing Office. March 2008. Available at: http://agingstats.gov/Agingstatsdotnet/Main_Site/Data/Data_2008.aspx. Accessed June 1, 2008.
41. Adler N, Rehkopf D. U.S. disparities in health: descriptions, causes, and mechanisms. Annu Rev Public Health 2008;29:235-252.
42. Wood J, Enser M, Fisher A, et al. Manipulating meat quality and composition. Proc Nutr Soc. 1999;58(2):363-370.
43. Davis D, Epp M, Riordan H. Changes in USDA food composition data for 43 garden crops, 1950 to 1999. J Am Coll Nutrition. 2004;23(6): 669-682.
44. Nestle M. Food marketing and childhood obesity—a matter of policy. N Engl J Med. 2006;354(24):2527-2529.
45. USDA. U.S. Food Consumption Up 16 Percent Since 1970. Available at http://www.ers.usda.gov/AmberWaves/November05/Findings/USFoodConsumption.htm. Accessed December 3, 2007.
46. Bente L, Gerrior S. Selected food and nutrient highlights of the 20th century: U.S. food supply series. Family Economics Nutrition Rev 2002;14(1):43-51.
47. USDA. U.S. Food Consumption Up 16 Percent Since 1970. Available at http://www.ers.usda.gov/AmberWaves/November05/Findings/USFoodConsumption.htm. Accessed December 3, 2007.
48. Gerrior S, Bente L. The nutrient content of the U.S. food supply, 1909-97. Home Economics Report. No. 54. U.S. Department of Agriculture, Center for Nutrition Policy and Promotion. 2001.
49. Simopoulos A. The importance of the omega-6/omega-3 fatty acid ratio in cardiovascular disease and other chronic diseases. Exp Biol Med (Maywood). 2008;233(6):674-688.
50. Willett W. The role of dietary n-6 fatty acids in the prevention of cardiovascular disease. J Cardiovasc Med (Hagerstown). 2007;8 Suppl 1:S42-45.
51. Willett W. Trans fatty acids and cardiovascular disease—epidemiologic data. Atheroscler Suppl. 2006;7(2):5-8.
52. Allport S. The Queen of Fats: Why Omega-3s Were Removed from the Western Diet and What We Can Do to Replace Them. Berkeley: University of CA Press; 2006.
53. Federal Interagency Forum on Aging-Related Statistics. Older Americans Update 2006: Key Indicators of Well-being. Washington, DC. US Government Printing Office. March 2006.
54. Cancer Statistics. National Cancer Institute. Available at: http://www.cancer.gov/statistics/. Accessed May 30, 2008.
55. Centers for Disease Control and Prevention. Overweight and obesity. Available at: http://www.cdc.gov/nccdphp/dnpa/obesity/. Accessed May 30, 2008.
56. Centers for Disease Control and Prevention. Overweight and obesity. Available at: http://www.cdc.gov/nccdphp/dnpa/obesity/trend/index.htm
57. US Dept of Health and Human Services. Available at http://www.healthypeople.gov/ Accessed July 21, 2008.
58. Ogden C, Carroll M, Flegal K. High body mass index for age among US children and adolescents, 2003-2006. JAMA. 2008; 299(20):2401-2405.
59. Centers for Disease Control and Prevention. Diabetes data and trends. Available at: http://apps.nccd.cdc.gov/DDTSTRS/default.aspx Accessed May 30, 2008.
60. Gale E. The rise of childhood type 1 diabetes in the 20th century. Diabetes. 2002;51(12):3353-3361. Available at http://www.medscape.com/viewarticle/445672_print
61. Centers for Disease Control and Prevention. Diabetes Projects. Available at: http://www.cdc.gov/diabetes/projects/cda2.htm. Accessed May 30, 2008.
62. Centers for Disease Control and Prevention. Achievements in Public Health, 1900-1999: Decline in Deaths from Heart Disease and Stroke -- United States, 1900-1999. Available at: http://www.cdc.gov/mmwr/preview/mmwrhtml/mm4830a1.htm. Accessed December 3, 2007.
63. Ford E, Ajani U, Croft J, Critchley J, et al. Explaining the decrease in U.S. deaths from coronary disease, 1980-2000. N Engl J Med. 2007;356(23):2388-2398.
64. Centers for Disease Control and Prevention. National Center for Heath Statistics. Available at: http://www.cdc.gov/nchs/fastats/lcod.htm Accessed July 5, 2008.
65. Centers for Disease Control and Prevention, National Center for Health Statistics. Health, United States, 2006, With Chartbook on Trends in the Health of Americans. Hyattsville, MD:2006. Available at: http://www.cdc.gov/nchs/data/hus/hus06acc.pdf. Accessed December 3, 2007.
66. Hajjar I, Kotchen T. Trends in prevalence, awareness, treatment, and control of hypertension in the United States, 1988-2000. JAMA. 2003;290:199-206.

FOOD *for* THOUGHT

Nature and Healthy Aging: Green is Good for Your Health

BURGEONING MOVEMENTS SUCH AS urban gardening, horticultural therapy, reconnecting kids with nature, and green roofs on office buildings are rooted in the reawakened understanding that the natural environment is good for the health of people and the planet.

A growing body of scientific evidence indicates that nature can help heal people's minds and bodies, and the benefits of both looking *at* nature and being *in* nature.

In settings where health is a top priority, such as hospitals, views of nature from hospital beds can speed healing, reduce need for pain medications, and improve mood. Healing gardens in hospitals are therapeutic for patients, visitors and health professionals alike. Looking at plants, trees and animals is good for mental and emotional health, and can even sustain attention. Interacting with nature is also a health tonic. Gardening reduces stress and builds social networks. Wilderness experiences are beneficial for cognitive disabilities and improve the self-esteem and wellbeing of inner city children. Jogging in the green outdoors seems to provide greater positive feelings than the same activity in a gym. Horticultural therapy can be a beneficial influence on everything from heart disease to dementia. The growing body of evidence suggests that people benefit so much both physically and mentally from contact with nature that it should be considered a public health strategy.[1 2]

The American Public Health Association (APHA) apparently agrees. A recent APHA article states that the "intersections between healthy people and a healthy environment are becoming clearer every day." Addressing the movement to reconnect kids with nature, a clarion call sounded by Richard Louv's book Last Child in the Woods: Saving Our Children from Nature-Deficit Disorder, the APHA notes that the recent trend away from outdoor play and activities is troubling both environmentalists and public health experts. It goes on to say that "experts predict that good health will be a major motivator in bringing families back to nature." [3]

Although bringing nature back into children's lives is a larger movement at present, in part because of the epidemic of obesity and other conditions linked to lack of exercise, we know major benefits also accrue to adults and elders from contacts with the natural world and exercise. This should become a priority in and around places where many aging people spend time, such as nursing homes, assisted-living facilities, and lower-income housing.

Economically distressed families and communities, who are already at greater risk of health problems, also tend to have less access to nature. We must ensure that urban environments include ample green spaces, parks, and safe playgrounds. (See chapter 2).

A growing body of scientific evidence indicates that nature can help heal people's minds and bodies.

Using the experience of nature as a prevention tactic makes good environmental and economic sense. There is a growing consensus that interdisciplinary dialogue and innovative social policy need to be fostered to advance efforts to once again bring nature into people's lives at home, at work, at school, and in health care facilities, especially for the neediest and most vulnerable members of our communities. However, "public health strategies are yet to maximize the untapped resource nature provides."[4]

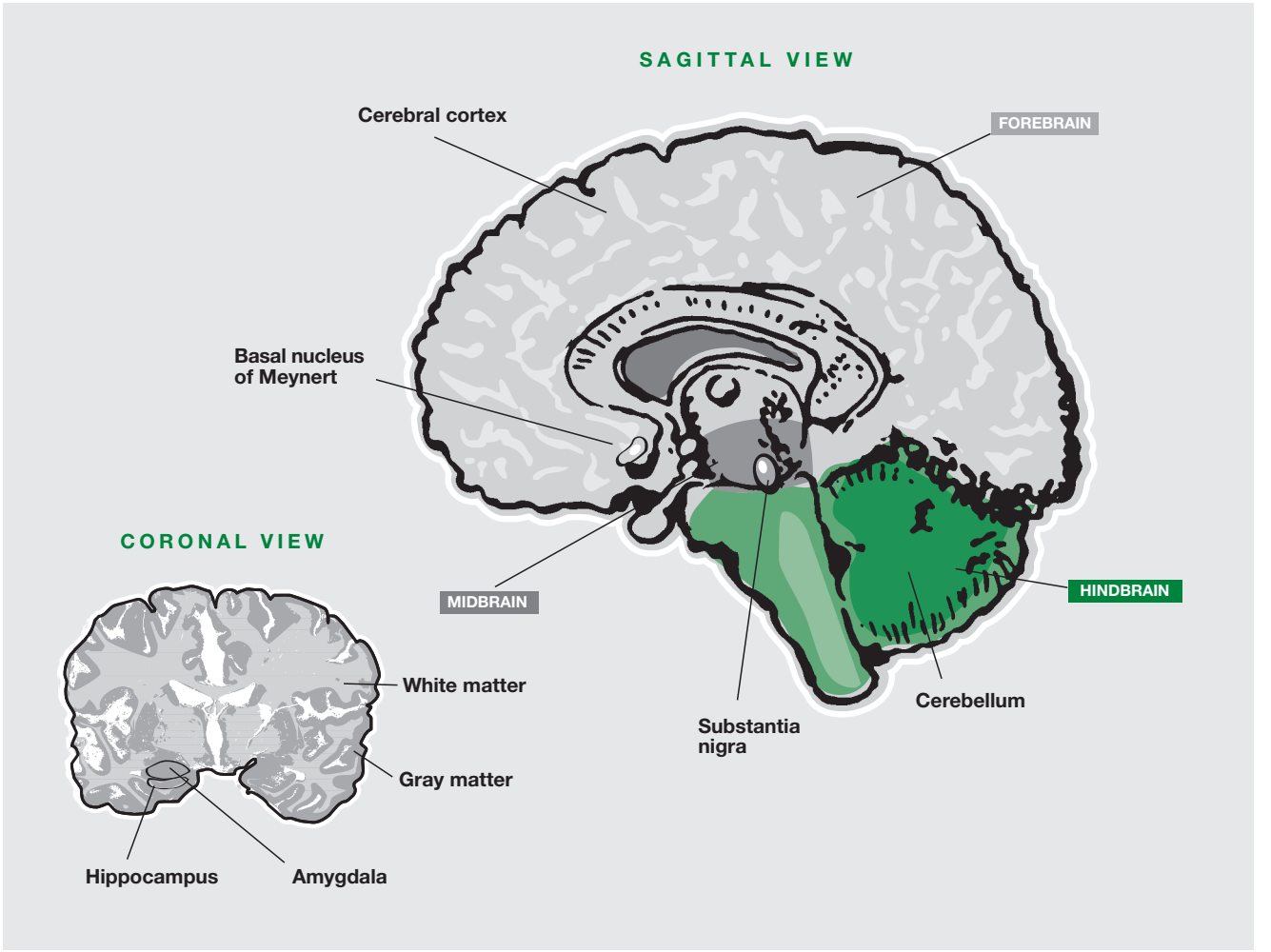
If we routinely plant the seeds of this prevention strategy, we can reap great rewards.

Resources:

Children and Nature Network:
http://www.cnaturenet.org/

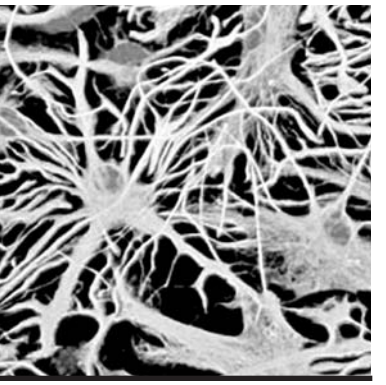
Endnotes

1. Frumkin H, Louv R. The powerful link between conserving land and preserving health. Land Trust Alliance Special Anniversary Report 2007. Available at: http://www.cnaturenet.org/resourcestools/FrumkinLouv.pdf. Accessed May 15, 2008.
2. St. Leger L. Health and nature—new challenges for health promotion. Health Promotion International 2003;18:173-175.
3. American Public Health Association. The Nation's Health. Washington DC. October 2007.
4. Maller C, Townsend M, Pryor A, St. Leger L. Healthy nature, healthy people: contact with nature as an upstream health promotion intervention for populations. Health Promotion International 2006; 21(1):45-54.



The diagrams above show the location of some key brain structures discussed in this report. The sagittal view shows a slice of the brain at about the midpoint as seen from the side. For instructional purposes, some structures are shown that are not technically visible at the mid point of the brain. The coronal diagram shows a slice through the forebrain viewed from the front. The diagrams show approximate locations only.

Chapter 3
A Primer on Brain Structure and Function



The brain is arguably the most complicated and least understood organ of the human body. Although much was accomplished in brain research during the 20th century, recent innovations in radiologic imaging, neurochemistry, neuroimmunology, genetics, and more have advanced our knowledge dramatically. We have learned, for instance, that adult brains are capable of creating new neurons, contrary to the conventional idea that humans are born with all the neurons they will ever have.[1] Modern imaging technology has allowed us to noninvasively observe patterns of neural activity during mental tasks, such as reading and adding numbers, so that we are beginning to get a much more dynamic view of structure and function.[2]

Modern imaging technology has allowed us to noninvasively observe patterns of neural activity during mental tasks.

Basic Neuroanatomy: Subsections of the Brain and Their Functions

The human brain can be anatomically divided into three broad regions: forebrain, midbrain, and hindbrain. The forebrain is the largest of these regions and contains the cerebral hemispheres, the areas most often associated with the unique cognitive abilities of humans. The cerebral hemispheres contain a number of deep-lying structures—including the basal ganglia, hippocampus, and amygdala—all enveloped in a wrinkled outer layer, the cerebral cortex.

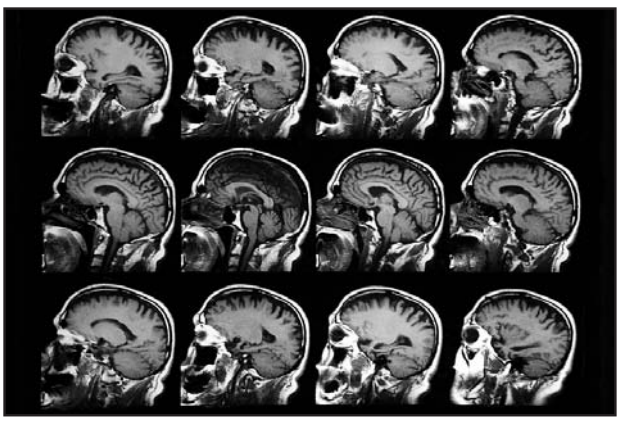
The basal ganglia, clusters of cells that act as hubs for neural signals, are involved in a broad range of functions from motor control to emotion and learning. The hippocampus is highly involved in memory, particularly in the formation of new memories about experienced events (or episodic memory), and may be one of the first regions to undergo changes in Alzheimer's disease. The amygdala is involved in emotional processing, particularly in attaching emotional associations to memories. Another forebrain structure, the basal nucleus of Meynert, is a center for the production of the neurotransmitter acetylcholine.

The first known written reference to the brain, this Ancient Egyptian hieroglyph was written around the 17th century BC.

Damage to either the gray matter of the cerebral cortex or the underlying white matter can produce specific cognitive deficits.

The tissue of the outer layer of the cerebral cortex consists mainly of neural cell bodies and is known as gray matter. Just beneath run neural projections that relay signals between cortical cells and virtually every other area of the brain. This tissue is known as white matter, owing to the myelin encasing the neural projections that makes it appear white to the naked eye. Damage to either the gray matter of the cerebral cortex or the underlying white matter can produce specific cognitive deficits. For example, lesions to Broca's or Wernicke's areas produce deficits in language expression and comprehension, respectively. Interruption of the white matter tracts connecting Broca's and Wernicke's areas produces more nuanced deficits in both language expression and comprehension.

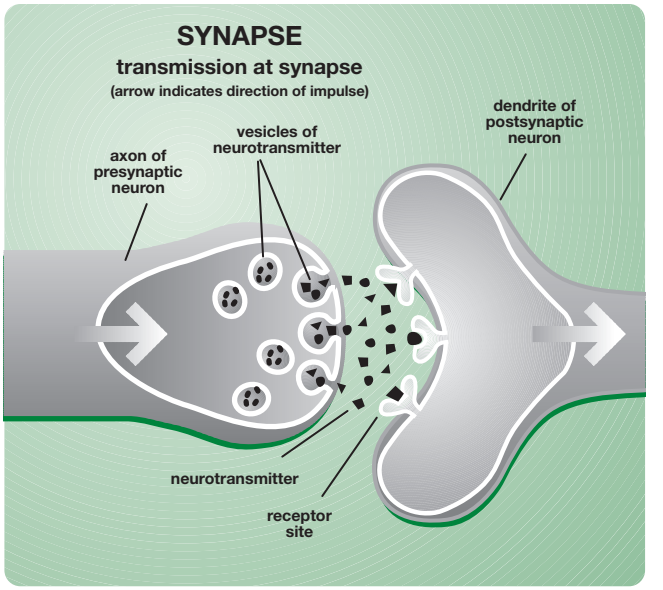
The midbrain and hindbrain are both smaller than the forebrain but regulate essential involuntary functions, such as heart rate and breathing. One hindbrain structure, the cerebellum, is also involved in movement and the learning of motor skills. Clusters of cells (nuclei) located in the midbrain and hindbrain produce essential neurotransmitters and interconnect with higher areas of the brain. These include the substantia nigra and raphe nuclei, which produce dopamine and serotonin, respectively. Both dopamine and serotonin have a wide range of effects on cognition, and dopamine in particular is involved in motor function. Since the nuclei of the midbrain and hindbrain are the centers of neurotransmitter production and interact with virtually every other part of the central nervous system, damage to any one of them can dramatically affect a host of neurological functions.



The Brain at the Cellular Level

The brain consists of roughly 100 billion neurons and an additional 1–5 trillion support cells known as glia. Estimating the exact number of cells in the brain has been difficult due in part to their sheer density. Neurons connect to one another at microscopic points of contact, known as synapses, where signals are transmitted through the release of neurotransmitters. Each individual neuron can have anywhere from a handful to several thousand synapses with other

neurons, putting the potential number of synapses in the brain in the hundreds of trillions.[3] Furthermore, synaptic connections are not static but can change depending on how frequently they are activated or in response to chemical signals in their environment, such as hormones or growth factors. It is this web of dynamic interconnections that is thought to underlie the brain's ability to orchestrate everything from unconscious activities, such as heart rate and breathing, to higher functions such as language, emotion, memory, and the ability to make conscious physical movements. Formation of new memories, in particular, is believed to be mediated by the modulation of synaptic connections.[4 5]



Neurotransmitters released into the synapse bind to receptor proteins embedded in the post-synaptic cell wall much like a key fitting into a lock. Once bound to the receptor, the neurotransmitter-receptor complex can change the cell's electrochemical state, making it more excited. If a neural cell becomes sufficiently stimulated, it will initiate a new neural impulse, which will then trigger the release of neurotransmitters at another synapse, where the process repeats.

Repeated activation can increase the strength of the synaptic connection between two neurons in a phenomenon known as long-term potentiation, so that an incoming neural impulse of the same strength will trigger a stronger response in the post-synaptic cell once the connection is potentiated. A similar phenomenon in which synaptic connections are weakened, known as long-term depression, can also occur. Long-term potentiation has been closely associated with performance in animal models of learning and memory, and presence of soluble amyloid-beta, a protein thought to be of importance in the development of Alzheimer's disease, has been shown to interfere with potentiation.[6]

The strengthening and weakening of synaptic connections is thought to be the most basic element of information processing in the brain, similar to the storage of 0s and 1s in a computer system. If we view the activation of a single synapse as analogous to the processing of one operation by a computer, and assume the brain has 100 billion neurons with an average of 10,000 synapses each that become activated

10 times per second, then the brain can perform a staggering 10 quadrillion (10^{16}) operations per second. By comparison, current high-end home computers perform around 20 billion operations per second, and the fastest supercomputer in the world as of June 2007 performed around 600 trillion (6×10^{14}) operations per second. In terms of this analogy, it would take about 17 supercomputers or half a million high-end personal computers to match the processing speed of a single healthy human brain. Thus, although it would be grossly inaccurate to state that brains and computers function in the same way, the human brain can nonetheless be viewed as a truly prolific information processor, owing in large part to its extensive web of interconnections. Loss of synapses—decreases in the brain's connections—occurs in many neurodegenerative conditions such as Alzheimer's disease.[7]

Glial Cells

When first discovered, these cells were thought simply to provide structural support for neurons by holding them in place and so were called "glia," Greek for "glue." Glial cells are now understood to play numerous vital roles in the brain. There are three main types of glial cells in the central nervous system, each with specific functions:

- Astrocytes help to regulate the neuronal environment by absorbing and releasing chemicals. They have been implicated in diverse roles ranging from participation in signal transmission to regulation of neuronal activity and synaptic network formation.
- Oligodendrocytes wrap neural extensions in myelin, a fatty insulating substance that greatly increases the speed at which neural impulses travel.
- Microglia perform immune functions in the brain and are extremely sensitive to signals in their surroundings that indicate distress.

Although the brain is normally protected from most pathogens by the blood-brain barrier, when infectious agents do enter the brain microglia react quickly in order to minimize damage to sensitive neuronal tissue. The microglial response to cellular distress signals is twofold, propagating distress signals to other microglia

through the release of chemical messengers and releasing cytotoxic chemicals that can lead to neural cell death. Cytotoxic chemicals include those that trigger apoptosis (programmed cell death), as well as other highly reactive chemicals such as hydrogen peroxide and nitric oxide that can directly damage cells. In other words, while microglia provide a quick reaction to infectious agents, the price of their rapid immune response can be the destruction of many healthy nerve cells.

Under normal circumstances, microglia facilitate brain reorganization, assisting in such tasks as synapse remodeling, controlled cell death, and the clearing of cellular debris. They are also important in regulating brain development and can exert neuroprotective effects through the release of anti-inflammatory chemicals and growth factors. However, microglia have many known pathological roles as well, most of which are thought to result from their chronic overactivation. One role that has gained significant notoriety is the selective destruction of dopamine-producing neurons through chronic and progressive inflammation in Parkinson's disease (see chapter 6).[8] In some cases, destruction of neurons can lead to further release of microglia-activating compounds, resulting in a vicious cycle of microglial activation and cell death. Chronic microglial activity has been implicated in the causation and development of Alzheimer's disease as well, and may also be involved in other forms of neurodegeneration including multiple sclerosis, amyotrophic lateral sclerosis, and Huntington's disease.[9]

HOW *it* WORKS

The Blood Brain Barrier

Cells lining the walls of blood vessels in the brain, as well as associated glial cells, participate in regulating the passage of chemicals into and out of the central nervous system, forming what is known as the blood-brain barrier. Astrocytes (a type of glial cell) physically contact blood vessels and can influence their activity and gene expression patterns through the release of chemical messengers. Although microglia are usually not considered part of the blood-brain barrier, they are both physically and functionally associated with it. Microglia do not perform any actual barrier function themselves but rather influence barrier properties through release of chemicals such as nitric oxide, interleukin 1–beta and tumor necrosis factor–alpha (see chapter 6). [11 12 13]

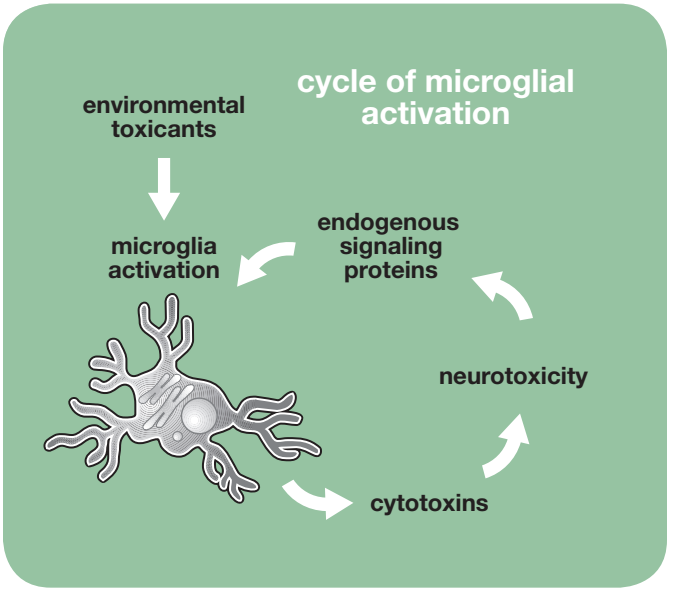
The selectivity with which the blood-brain barrier regulates the passage of substances into and out of the brain changes under different conditions. For instance, permeability increases markedly under conditions of oxygen and glucose deprivation, as well as in response to proinflammatory biochemical signals. During development, higher permeability can allow toxicants into the developing brain. Dysfunction of the blood-brain barrier also commonly occurs at the other end of the lifespan, and higher levels of permeability have been correlated with more rapid progression of dementia. However, while changes in blood-brain barrier permeability are associated with dementia, their significance in the disease process is still unclear.

Neurologic Changes in Alzheimer's and Parkinson's Diseases

Typically, dementia first affects the forebrain structures involved in memory and judgment and then progresses to hindbrain structures that regulate balance and coordination. While virtually every region of the brain may sustain some form of damage in neurodegenerative disease, certain areas appear to undergo pathological changes more frequently than others. As the structure most commonly associated with memory, damage to the hippocampus is generally considered to result in some of the first clinical symptoms of Alzheimer's disease. Studies of human patients as well as controlled studies in animals have demonstrated that hippocampal damage produces profound deficits in spatial navigation and episodic memory.[14]

The basal nucleus of Meynert is another brain structure that is commonly affected in neurodegenerative disease. Damage to this area has classically been associated with Alzheimer's disease[15] but is common in other forms of neurodegeneration as well.[16]

Since the basal nucleus of Meynert is a central part of the brain's acetylcholine system, the loss of neurons in this area deprives higher brain regions of acetylcholinergic input. The neurotransmitter acetylcholine has known roles in learning and memory and has been shown to play a role in long-term potentiation.[17] Animal studies show that damaging acetylcholine-producing neurons in the basal nucleus of Meynert and damaging the higher cortical areas to which they connect yield similar behavioral impairments.[18] Pharmacologically blocking acetylcholine activity has negative effects on measures of



Certain substances from the nutritional and chemical environment are able to cross the blood-brain barrier and trigger microglial activation. When activated, microglia attempt to eliminate the perceived threat by releasing cytotoxic chemicals that may also damage neurons, which in turn can lead to the release of more microglia-activating compounds.

cognitive performance,[19] and most medications that have been shown to temporarily improve cognitive function in Alzheimer's disease work by increasing brain levels of acetylcholine. Thus, it is not surprising that the loss of a neurotransmitter so intimately involved in learning, memory, and cognition would be a common finding in dementia.

Loss of dopamine-producing neurons in the substantia nigra is a cardinal feature of Parkinson's disease. As cells in this region normally project to parts of the basal ganglia which in turn project to several other higher brain regions, their loss also has widespread effects on brain function. Among the most notable of these effects is loss of the ability to execute voluntary movements, the primary symptom of Parkinson's disease. Among other cognitive processes, dopamine signaling is involved in attention, memory, and motivation. It has also been extensively studied for its roles in the brain's pleasure systems and addiction. Abnormal dopaminergic signaling is thought to explain the compulsive risk-seeking behaviors (such as compulsive gambling) that occur in a subset of medicated Parkinson's patients.[20] While dopaminergic dysfunction is of central importance in movement disorders, it may be a factor in cognitive impairment as well.[21]

Other neurotransmitter systems such as serotonin, glutamate, and norepinephrine also show some evidence of involvement in neurodegenerative disease. Although discussing the roles of each system in these disorders is beyond the scope of this chapter, it is worth noting that deficits in multiple neurotransmitter systems may interact synergistically to affect cognition. Furthermore, changes in the expression of neurotransmitter receptors and other factors that affect neural communication may also be important in age-associated cognitive impairment.

Pathological Markers of Neurodegenerative Disease

Post-mortem studies of the brains of patients with neurodegenerative diseases often show characteristic abnormalities, known as pathological markers. While they do not show the whole picture of what has gone wrong in a cognitively impaired brain, these abnormalities are considered to be the microscopic physical manifestations of the disease process.

Conventional definitions of neurodegenerative diseases often suggest that each one has a circumscribed set of pathological features. For example, Alzheimer's disease is said to be characterized by amyloid plaques and neurofibrillary tangles, and Parkinson's disease

by Lewy bodies. In reality, however, pathology is often spread across a spectrum, with significant overlap in pathological markers and cognitive symptoms across many supposedly distinct disease states. The notion of a continuum of pathological and cognitive features in neurodegenerative disease is further addressed in chapter 5.

Amyloid plaques, the principle pathological marker of Alzheimer's disease, consist of aggregates of a small protein known as amyloid-beta. While normally produced throughout the body and potentially playing some important physiological roles at low concentrations, increased amyloid-beta levels in Alzheimer's disease lead to the formation of insoluble aggregates in the brain. These aggregates, also known as senile plaques, in turn seem to be associated with damage to nearby brain cells and microglial activation.

Neurofibrillary tangles are the second pathological hallmark of Alzheimer's disease and consist of a modified structural protein known as tau. Neurofibrillary tangles and other abnormal tau aggregates also occur across a spectrum of other neurodegenerative conditions, such as frontotemporal dementia and multiple system atrophy. Under normal circumstances tau proteins assist in stabilizing the structure of the neuron, but in disease states they may stick to one another inappropriately, leading to cellular dysfunction. Although the links between neurofibrillary tangles and amyloid plaques are unclear, they tend to appear together in Alzheimer's disease and may both be necessary for cognitive impairment to occur.

Lewy bodies are a third type of pathological marker comprised of intracellular aggregates of the protein alpha-synuclein as well as an assortment of other proteins. While the physiological function of alpha-synuclein has yet to be explained, it tends to be concentrated around synapses and may be involved in cell structure arrangement.[22] Although best known for their appearance in the substantia nigra in most cases of Parkinson's disease, Lewy bodies have also been found in several other forms of neurodegeneration, and distinct cortical and subcortical types have been recognized. While it is still not clear what causes the formation of Lewy bodies, they may result from the buildup of waste products when cellular protein recycling mechanisms stop functioning properly.[23]

Even though pathological markers are often associated with cellular dysfunction in the brain, they should not necessarily be thought of as the drivers of the disease process. Pathological markers

Even though pathological markers are often associated with cellular dysfunction in the brain, they should not necessarily be thought of as the drivers of the disease process.

usually appear as parts of feedback loops in which their formation contributes to cellular dysfunction, which in turn contributes to their formation. However, they may not be the initiators of these vicious cycles. Instead, systemic conditions and environmental influences may well create the conditions for these processes to occur and, perhaps in the setting of susceptibility genes, provide the impetus to set them into motion. We discuss the conditions of oxidative stress and inflammation as key factors in these processes in chapter 6.

Normally, the brain maintains its function well into the late years of life even though structural changes associated with normal aging may be present. Neuroscientists have described considerable plasticity in the aging brain that permits recruitment of new pathways to accomplish neurological functions when older, well established pathways no longer work as well as they once did because of the normal aging process.

The next chapter summarizes general physiologic changes associated with normal aging and considers the aging brain in the context of total life history. Distinguishing changes associated with normal aging from those that are the manifestations of neurodegenerative disease is often difficult and subject to considerable debate.

Endnotes

1. Gage F. Neurogenesis in the adult brain. J Neurosci. 2002;22(3):612-613.
2. Ogawa S, Tank DW, Menon R, et al. Intrinsic signal changes accompanying sensory stimulation: functional brain mapping with magnetic resonance imaging. Proc Natl Acad Sci USA. 1992;89(13):5951-5955.
3. Drachman, DA. Do we have brain to spare? Neurology. 2005;64:2004-2005.
4. Bliss T, Collingridge G, Laroche S. ZAP and ZIP, a story to forget. Science. 2006;313:1058-1059.
5. Whitlock J, Heynen AJ, Shuler MG, et al. Learning induces long-term potentiation in the hippocampus. Science. 2006;313:1093-1097.
6. Chen QS, Kagan BL, Hirakura Y, et al. Impairment of hippocampal long-term potentiation by Alzheimer amyloid beta-peptides. J Neurosci Res. 2000;60(1):65-72.
7. Terry RD, Masliah E, Salmon DP, et al. Physical basis of cognitive alterations in Alzheimer's disease: synapse loss is the major correlate of cognitive impairment. Ann Neurol. 1991;30:572-580.
8. Gao H, Jiang J, Wilson B, et al. Microglial activation-mediated delayed and progressive degeneration of rat nigral dopaminergic neurons: relevance to Parkinson's disease. J Neurochem. 2002;81:1285-1297.
9. Block ML, Zecca L, Hong JS. Microglia-mediated neurotoxicity: uncovering the molecular mechanisms. Nat Rev Neurosci. 2007;8:57-69.
10. Bowman GL, Kaye JA, Moore M, et al. Blood-brain barrier impairment in Alzheimer disease: stability and functional significance. Neurology. 2007;68:1809-1814.
11. Block ML, Zecca L, Hong JS. Microglia-mediated neurotoxicity: uncovering the molecular mechanisms. Nat Rev Neurosci. 2007;8:57-69.
12. Yamagata K, Tagami M, Takenaga F, et al. Hypoxia-induced changes in tight junction permeability of brain capillary endothelail cells are associated with IL-1beta and nitric oxide. Neurobiol Dis. 2004;17:491-499.
13. Mark KS, Miller DW. Increased permeability of primary cultured brain microvessel endothelial cell monolayers following TNF-alpha exposure. Life Sci. 1999;64:1941-53.
14. Verhaeghen P, Marcoen A, Goossens L. Facts and fiction about memory aging: A quantitative integration of research findings. J Gerontol. 1993;48:157-171.
15. Whitehouse PJ, Price DL, Struble RG, et al. Alzheimer's disease and senile dementia: loss of neurons in the basal forebrain. Science. 1982;215(4537):1237-1239.
16. Samuel W, Alford M, Hofstetter CR, et al. Dementia with Lewy bodies versus pure Alzheimer disease: differences in cognition, neuropathology, cholinergic dysfunction, and synapse density. J Neuropathol Exp Neurol. 1997;56(5):499-508.
17. McKay BE, Placzek AN, Dani JA. Regulation of synaptic transmission and plasticity by neuronal nicotinic acetylcholine receptors. Biochem Pharmacol. 2007;74(8):1120-1133.
18. Muir JL. Acetylcholine, Aging, and Alzheimer's Disease. Pharmacol Biochem Behav. 1997;56(4):687-696.
19. Muir JL. Acetylcholine, Aging, and Alzheimer's Disease. Pharmacol Biochem Behav. 1997;56(4):687-696.
20. Imamura A, Uitti RJ, Wszolek ZK. Dopamine agonist therapy for Parkinson disease and pathological gambling. Parkinsonism Relat Disord. 2006;12(8):506-508.
21. Kaasinen V and Rinne JO. Functional imaging studies of dopamine system and cognition in normal aging and Parkinson's disease. Neurosci Biobehav Rev. 2002;26:785-793.
22. Alim MA, Ma QL, Takeda K, et al. Demonstration of a role for α-synuclein as a functional microtubule-associated protein. J Alzheimers Dis. 2004;6(4):435-442.
23. Olanow CW, Perl DL, DeMartino GN, et al. Lewy-body formation is an aggresome-related process: a hypothesis. Lancet Neurol. 2004;3(8):496-503.

Chapter 4

An Arc Across the Lifespan: From the Beginning

Virtually all biological systems normally undergo functional changes with aging, and the brain is no exception. We can think of age-related changes in brain function as being on the trajectory of an arc that begins decades earlier during fetal development. At any age, distinguishing normal variations in brain function from pathological conditions is sometimes challenging and can be especially difficult in later years. Individual differences in the timing, nature, and extent of functional decline are common. Social perceptions can also influence how we interpret obvious abnormalities in brain function. Neurologist Peter J. Whitehouse notes, "Our concepts of Alzheimer's disease moved from a social model before the turn of the 19th century to a focus on biology in the early 1900s, to a return to psychosocial aspects in mid-century, and then again to the current biological focus at the end of the 20th century."[1]

Individual differences in the timing, nature, and extent of functional decline are common.

Age-related changes in brain function must also be considered within the context of more general biological and social health. Aging inevitably includes changes in the physiologic functions of most systems of the body. Ultimately, of course, aging leads to loss of resilience and increased vulnerability to disease, finally resulting in functional losses that are incompatible with life, and death follows.

Physiologic Changes Associated with Normal Aging

Chinese symbol for longevity

Fetuses, infants, and children acquire functional capacities at various times during development. For example, different metabolic systems come on line throughout fetal development and infancy. Lung function is not fully developed until young adulthood. Reproductive functional development begins in the fetus and infant, undergoes a period of latency, and is reawakened in puberty.

Toward the other end of the arc, as people age genetic and other kinds of chromosomal damage increase while cellular repair

responses decrease. Renal blood flow and kidney function decline. Motility of portions of the intestinal tract decreases, as does gastric acid secretion. Combined with decreased intake of nutrients in the elderly, these changes may result in malnutrition.[2] Some liver enzymes responsible for metabolizing pharmaceuticals and other foreign chemicals or environmental contaminants are reduced in the elderly.[3] Consequently, the toxicity of chemical agents can be enhanced or, on occasion, reduced if metabolic activation by enzymes is necessary to form a more toxic substance. Levels of many hormones decline with age, sometimes dramatically as during menopause. The function of the blood-brain barrier also declines with age, allowing blood-borne toxicants to acquire previously restricted access to brain tissue.[4] Thus, as the brain ages it may also become more vulnerable to environmental factors that contribute to further degeneration.

As the brain ages it may also become more vulnerable to environmental factors that contribute to further degeneration.

It is also important to consider the influences of genetics and a lifetime of social and environmental influences in order to understand the timing and severity of functional declines and vulnerabilities in later life.

The Natural History of Brain Development and Aging

Brain Development

Brain development begins soon after conception and continues into young adulthood. In the fetus, cells in the brain proliferate, migrate to their appropriate positions, and differentiate into various specialized cell types. Complex networks of neurons are connected through synapses, many of which are normally pruned in early childhood. Many nerve fibers are coated with a sheath of fat-containing myelin that facilitates nerve transmission. Myelination in

the fetal brain begins during the later stages of pregnancy and continues throughout childhood and the teen age years.

During the first few years of life, children develop motor skills (rolling over, standing, walking) and begin to understand and express language. Later they begin to regulate attention and emotional expression; improve motor coordination, visual processing, and visual-spatial skills; and develop more complex information processing.

With the onset of puberty the brain undergoes further transformation under the influence of sex hormones. New axons and dendrites elaborate from neurons. New neural connections develop while others are pruned back. Further myelination results in a net increase in the ratio of white-to-gray matter.[5] These changes ultimately contribute to further development of abstract thinking, organizational and planning skills, and the ability to store and retrieve information and make decisions in early adulthood.

Factors that converge to affect this trajectory of skill acquisition include genetic inheritance; maternal nutrition during pregnancy and nutrition throughout infancy, childhood, and early adulthood; the quality of the social environment; education; and the presence or absence of exposures to toxic agents, infections, illnesses, or injuries that can interfere with normal brain development.

A considerable amount of plasticity (the ability to physically and functionally change and adapt) is inherent in the brain, ensuring some capacity to cope with or buffer challenges to normal development. But that plasticity is also limited and studies show that damage resulting from exposure to neurodevelopmental toxicants, such as lead, sometimes in combination with micronutrient deficiencies and compromised social circumstances, can only partially be alleviated.[6] [7] Consequently, early life events or circumstances can have enduring impacts on adult cognitive abilities and behavior.[8]

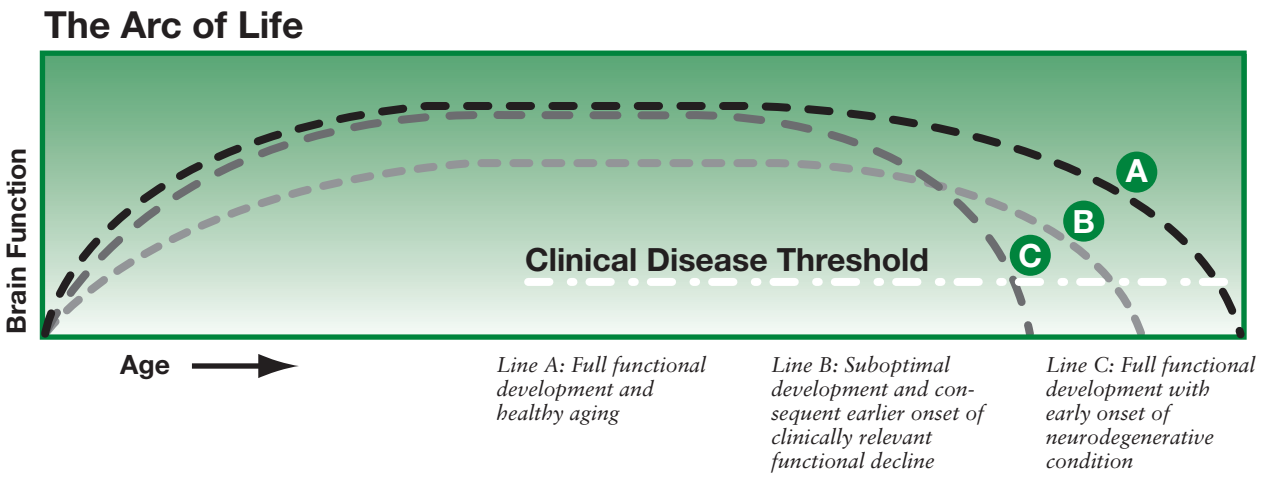
The capacity of the brain to change and adapt is not confined to periods of early development. Learning and memory throughout life are based primarily on the strengthening of synaptic function or structural changes that occur in response to experience.[9] Neuroscientists have shown that the adult brain is even capable of generating new neurons from primitive stem cells in some areas, overturning long-held dogma that this was impossible.[10] Compensatory mechanisms can counteract age-related declines in brain function.[11] These observations are important when considering strategies for delaying the onset or slowing cognitive decline in later years. We will return to this later.

Healthy Brain Aging

As healthy people age, declines in cognitive function and other evidence of neurological degeneration become increasingly likely. This occurs in virtually everyone although some people experience altered brain function at an earlier age or at a faster rate than others. The reasons for this variability are not always well understood, but in addition to genetic susceptibility factors such as hypertension, poor nutrition, excessive alcohol ingestion, lack of exercise, and stress can increase the rate and extent of cognitive decline.[12] Hormonal changes during normal aging are also likely to play a role.

Distinguishing the cognitive decline of normal aging from that due to various pathological processes, including Alzheimer's disease, is an ongoing challenge. Memory impairment in tasks that rely on attention and controlled processing of information is common with normal aging.[13] [14] In particular, memory necessary for the acquisition and processing of new information, as well as memory necessary for holding information during processing, tend to decline with age.[15] Some kinds of learning, particularly those that require speed and motor coordination, become increasingly difficult with age.[16] These impairments are associated with volume loss and depletion of certain neurotransmitters in the frontal region of the brain. The number of synapses and synaptic function in some areas of the brain also diminish with advancing age.[17] [18] Receptors for the neurotransmitter glutamate decrease in synaptic junctions, contributing to decline in synapse function.[19] Levels of neurotransmitters, including dopamine and acetylcholine, also decline in several areas of the brain.[20]

It would be a mistake, however, to conclude that normal brain aging inevitably results in inalterable, steadily declining function. Recent studies in animals and humans show that retained plasticity enables aging brains to acquire or reacquire motor and cognitive skills. The mechanisms and brain circuitry involved, however, may be quite different from those used for skill acquisition during brain development.[21] [22]



In summary, we can think of an arc of brain development and function that begins soon after conception and progresses along a trajectory into adulthood and older age. The shape of that trajectory—its features, length, and rate of change—can be profoundly influenced by many interacting genetic and environmental factors encountered throughout the lifespan.

Early Life Events and the Developmental Basis of Adult Neurodegenerative Disease

Brain Reserve

Neuroscientists generally acknowledge the likelihood that, in many people, neurodegenerative conditions—whether the normal cognitive impairment of aging, relentlessly progressive Alzheimer's disease, or Parkinson's disease—may be initiated decades before symptoms become apparent.[23] However, the timing of the onset and progression of symptoms may be influenced by brain "reserve"—delayed in people with more reserve and accelerated in those with less. This means the onset of symptoms due to a neurodegenerative condition could conceivably be delayed either by slowing down the pathological process or by increasing brain reserve.

The idea of brain reserve took hold in the 1980s after an autopsy study of nursing home residents with and without dementia.[24] It showed that the brains of some elderly people without signs of dementia before death had abundant plaques and tangles, hallmarks of Alzheimer's disease, but without the typical loss of neurons and brain volume. This suggested either that they had somehow

Epigenetics

Epigenetics refers to modifications to genes, other than changes in the DNA sequence, that influence gene expression. These modifications can include adding molecules, such as methyl groups, to the DNA backbone of a gene or altering histones, which are proteins associated with the gene. RNA interference with gene expression is a third mechanism. The end result of epigenetic changes is alteration of the pattern of protein synthesis under the control of the involved gene. Recent evidence suggests that some epigenetic changes are heritable from one generation to the next, showing how environmental factors that alter gene expression in an individual can also influence gene expression in his or her descendant generations.

escaped the neuronal loss seen in most cases of Alzheimer's disease or that they began with a larger initial reserve of neurons.

Additional studies have confirmed that some individuals have dementia without extensive pathological findings, while others have extensive pathology without much cognitive impairment. In a recent effort to understand these discrepancies, 81 patients with the diagnosis of Alzheimer's disease and no other recognizable reasons for their cognitive decline were carefully evaluated in order to quantify the extent of their dementia.[25] Following their deaths, the researchers examined their brains for pathological changes. They concluded that there was a fairly close correlation between the numbers of plaques and tangles in brain tissue and the degree of dementia in people who had early-onset Alzheimer's disease, but the correlation became less prominent in older people. These findings are consistent with the hypothesis that the manifestations of Alzheimer's disease in older people are more likely to be influenced by multiple interacting factors such as vascular disease and reduced blood flow, social isolation, undernutrition, and so on. Whether or not early-onset and late-onset Alzheimer's are fundamentally different in other ways is not known. But a variety of factors, including nutrition, experience, education, and social support, have been proposed as contributing to brain reserve and building resilience to disease or age-related declines in function.

The Barker Hypothesis and Early Origins of Adult Disease

The related concepts of early origins of adult disease and building resilience to reduce disease risk have strong support in other areas

of clinical medicine. In the 1980s, David Barker and colleagues from the UK published an influential study of a large cohort of individuals in which they noted that low-birthweight babies were at increased risk of heart disease as adults, even when other known risk factors were taken into account.[26] Barker theorized that somehow growth restriction in utero set the stage for subsequent adult heart disease. These findings spurred considerable interest in the concept of the fetal (or developmental) origins of adult disease. Most attention has been given to the impacts of fetal, infant, and childhood nutrition on subsequent risks of cancer, diabetes, obesity, and cardiovascular disease. It remains unclear whether birthweight or subsequent "catch-up" growth is the important risk determinant for heart disease. Nonetheless, a growing body of evidence now points to the important influence of early life events on subsequent disease risk.

More recently, a limited but growing body of evidence is beginning to point to developmental origins of neurodegenerative conditions, including Alzheimer's disease and Parkinson's disease.[27] [28] [29] The brain reserve hypothesis proposes that early life exposures to environmental chemicals, inadequate nutrition, or other environmental stressors, alone or in combination, can reduce the number of neurons, alter levels of neurotransmitters, or reduce synaptic density in critical areas of the brain. Clinical symptoms of neurological disease then emerge much later in life when these abnormal changes combine with normal declines in cell numbers and function.[30] [31]

The developmental origins of adult disease can also be mediated through epigenetic mechanisms in which gene expression is altered by environmental variables without any mutational change in the DNA sequence (see sidebar previous page.).

Modified gene expression alters the production of proteins under control of that gene. In brain tissue, where neurons have an extremely long lifespan, life-long effects from gene expression altered

Widespread changes in modern, industrial society… created the conditions for an explosion of neurodegenerative diseases in the aging population.

during development are entirely plausible. Animal studies show that early life exposure to lead, for example, can strongly influence the expression of a gene responsible for producing a protein involved in Alzheimer's disease much later in life[32] (see chapter 7). The same level of lead exposure in the adult animal does not have the same effect on gene expression.

Other conditions that may develop early or at any time throughout the lifespan and that increase the risk of developing Alzheimer's disease or other kinds of dementia include hyperinsulinemia, insulin resistance, diabetes, obesity, and others that feature up-regulation of inflammatory markers.[33] [34] The science underlying this cluster of relationships is discussed in chapter 6 and should raise a warning flag among public health officials and decision-makers at every level—from school boards to city planners to Congress. As we have noted, health-trend tracking in the U.S. and many other countries consistently shows increases in the prevalence of diabetes, obesity, and a variety of other chronic diseases characterized at least in part by inflammation. Widespread changes in modern, industrial society largely responsible for the changing pattern of disease have also created the conditions for an explosion of neurodegenerative diseases in the aging population. We have only begun to get a glimpse of what is to come if we do not act on what we already know. As we discuss in more detail in chapter 9, these patterns of disease clearly suggest opportunities for their primary prevention.

Endnotes

1. Whitehouse P. History and the future of Alzheimer disease. In: Whitehouse P, Maurer K, Ballenger J., eds. Concepts of Alzheimer Disease: Biological, Clinical, and Cultural Perspectives. Baltimore, MD: Johns Hopkins Univ. Press; 2000.
2. Saltzman J, Russell R. The aging gut: nutritional issues. Gastroenterol Clin North Amer. 1998;27(2):309-324.
3. Schmucker D. Age-related changes in liver structure and function: implications for disease? Exp Gerontol. 2005;40(8-9):650-659.
4. Bartels A, Kortekaas R, Bart J, et al. Blood-brain barrier P-glycoprotein function decreases in specific brain regions with aging: a possible role in progressive neurodegeneration. Neurobiol Aging. 2008 Mar 19. (Epub ahead of print)
5. Sisk C, Zehr J. Pubertal hormones organize the adolescent brain and behavior. Front Neuroendocrinol. 2005;26(3-4):163-174.
6. Ruff H, Bijur P, Markowitz M, Ma Y, Rosen J. Declining blood levels and cognitive changes in moderately lead-poisoned children. J Am Med Assoc. 1993;269:1641-1646.
7. Hubbs-Tait L, Nation J, Krebs N, Bellinger D. Neurotoxicants, micronutrients. and social environments: individual and combined effects on children's development. Psychological Science in the Public Interest. 2005;6(3):57-121.
8. Needleman H, McFarland C, Ness R, Fienberg S, Tobin M. Bone lead levels in adjudicated delinquents: a case control study. Neurotoxicol Teratol. 2002;24(6):711-717.
9. Benfenati F. Synaptic plasticity and the neurobiology of learning and memory. Acta Biomed. 2007;78 Suppl 1:58-66.
10. Gage F. Neurogenesis in the adult brain. J Neuroscience. 2002;22(3):612-613.
11. Heuninckx S, Wenderoth N, Swinnen S. Systems neuroplasticity in the aging brain: recruiting additional neural resources for successful motor performance in elderly persons. J Neurosci. 2008;28(1):91-99.
12. Raz N, Rodrigue K. Differential aging of the brain: patterns, cognitive correlates and modifiers. Neurosci Biobehavioral Rev. 2006;30:730-748.
13. Buckner R. Memory and executive function in aging and AD: multiple factors that cause decline and reserve factors that compensate. Neuron. 2004;44:195-208.
14. Howieson D, Camicioli R, Quinn J, et al. Natural history of cognitive decline in the old. Neurology. 2003;60(9):1489-1494.
15. Small S, Stern Y, Tang M, Mayeux R. Selective decline in memory function among healthy elderly. Neurology. 1999;52(7):1392-1396
16. Mahncke H, Bronstone A, Merzenich M. Brain plasticity and functional losses in the aged: scientific bases for a novel intervention. Prog Brain Res. 2006;157:81-109.
17. Masliah, E, Mallory, M; Hansen, L; et al. Quantitative synaptic alterations in the human neocortex during normal aging. Neurology. 1993;43(1):192-197.
18. Hof P, Morrison J. The aging brain: morphomolecular senescence of cortical circuits. Trends Neurosci. 2004;27(10):607-613.
19. Hof P, Morrison J. The aging brain: morphomolecular senescence of cortical circuits. Trends Neurosci. 2004;27(10):607-613.
20. Raz N, Rodrigue K. Differential aging of the brain: patterns, cognitive correlates and modifiers. Neurosci Biobehavioral Rev. 2006;30:730-748.
21. Dinse H. Cortical reorganization in the aging brain. Prog Brain Res. 2006;157:57-80.
22. Heuninckx S, Wenderoth N, Swinnen S. Systems neuroplasticity in the aging brain: recruiting additional neural resources for successful motor performance in elderly persons. J Neurosci. 2008;28(1):91-99.
23. Borenstein A, Copenhaver C, Mortimer J. Early-life risk factors for Alzheimer disease. Alzheimer Dis Assoc Disord. 2006;20(1):63-72.
24. Katzman R, Terry R, DeTeresa R, et al. Clinical, pathological, and neurochemical changes in dementia: a subgroup with preserved mental status and numerous neocortical plaques. Ann Neurol.1988;23(2):138-144.
25. Prohovnik I, Perl D, Davis K, Libow L, Lesser G, Haroutunian V. Dissociation of neuropathology from severity of dementia in late-onset Alzheimer disease. Neurology. 2006;66(1):49-55.
26. Barker D, Winter P, Osmond C, Margetts B, Simmonds S. Weight in infancy and death from ischaemic heart disease. Lancet. 1989;2(8663):577-580.
27. Barlow B, Cory-Slechta D, Richfield E, Thiruchelvam M. The gestational environment and Parkinson's disease: evidence for neurodevelopmental origins of a neurodegenerative disorder. Reprod Toxicol. 2007 Apr-May;23(3):457-70.
28. Zawia N, Riyaz Basha M. Environmental risk factors and the developmental basis for Alzheimer's disease. Rev Neurosciences. 2005;16:325-337.
29. Borenstein A, Copenhaver C, Mortimer J. Early-life risk factors for Alzheimer disease. Alzheimer Dis Assoc Disord. 2006;20(1):63-72.
30. Langston J, Forno L, Tetrud J, Reeves A, Kaplan J, Karluk D. Evidence of active nerve cell degeneration in the substantia nigra of humans years after 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine exposure. Ann Neurol. 1999;46(4):598-605.
31. Weiss B, Clarkson T, Simon W. Silent latency periods in methylmercury poisoning and in neurodegenerative disease. Environ Health Perspect 110 suppl. 2002;5:851-854.
32. Zawia N, Riyaz Basha M. Op. cit.
33. Borenstein A, Copenhaver C, Mortimer J. Early-life risk factors for Alzheimer disease. Alzheimer Dis Assoc Disord. 2006;20(1):63-72.
34. Whitmer R, Gunderson E, Quesenberry C, Zhou J, Yaffe K. Body mass index in midlife and risk of Alzheimer disease and vascular dementia. Curr Alzheimer Res. 2007;4(2):103-109.

Still Healthy at 100 – What's the Secret?

IT MAY BE NO SECRET at all, but good genes combined with the old-fashioned values of eating well and in moderation, hard work, community spirit, and faith foster the health of the longest-lived among us.

Good genes combined with the old-fashioned values of eating well and in moderation, hard work, community spirit, and faith foster the health of the longest-lived among us.

The centenarians of the Japanese prefecture of Okinawa are among the healthiest elders in the world. The Okinawa Centenarian Study, the world's longest-running population-based study of centenarians and now in its 29th year, has revealed a broad range of lifestyle characteristics that are likely contributing to amazing health well into later years. (They really are that old; ages were validated recently.[1]) The study has concentrated on genetics, diet, exercise habits, and psychospiritual beliefs and practices.

The Okinawans typically are optimistic, adaptable, and easy-going. They value spirituality and social engagement. They consume a diet rich in vegetables, fiber, flavonoids, and good fats, including omega-3s. These centenarians have been lean throughout their long lives, eating a low-calorie, low-glycemic-load diet. They limit food intake in a cultural practice known as *hara hachi bu,* literally "stomach 80 percent full," and keep physically active via a variety of daily activities. Compared to North Americans, they have lower rates of dementia, certain cancers such as breast and prostate, osteoporosis, and cardiovascular disease.[2]

Many of these lifestyle characteristics have been found in other, less studied populations. The Blue Zones project has been taking scientists around the world for the past five years to investigate where people live the healthiest long lives. Among Blue Zone inhabitants are a group of elders on the Nicoyan peninsula of Costa Rica who chop wood, ride bicycles, and grind corn by hand, and mountain people in Sardinia, Italy, whose secrets include "wine with staggering levels of antioxidants and a tradition of celebrating old age."

The Blue Zone researchers have identified common denominators for healthy aging that are consistent with many of the findings from the Okinawa study. They include:

- regular physical movement incorporated into everyday activities,
- good community and family relationships,
- eating well (and less) and drinking wine each day, and
- a sense of purpose in life as well as a centered and calm outlook.

The practices of the Costa Rican elders reflect these—they eat fewer calories, enjoy physical work in daily chores, maintain social networks, and have a strong sense of purpose.[3 4]

The New England Centenarian Study at Boston Medical Center also points to certain activities and characteristics. Its "Predictors of Reaching 100" list notes that few centenarians are obese and that substantial smoking history is rare. A preliminary study suggests that centenarians are better able to handle stress than the majority of people.

Good genes do help. The New England study found that at least half of centenarians have parents, siblings, or grandparents who have also achieved very old age.[5]

Endnotes

1 Willcox DC, Willcox BJ, He Q, Wang NC, Suzuki M. They really are that old: a validation study of centenarian prevalence in Okinawa. J Gerontol A Biol Sci Med Sci. 2008 Apr;63(4):338-49.

2 Okinawa Centenarian Study. Available at: http://www.okicent.org/. Accessed June 19, 2008.

3 Blue Zones. Available at: http://www.bluezones.com/home/. Accessed June 17, 2008.

4 Buettner D. Living Healthy to 100. AARP Magazine May/June 2008.

5 The New England Centenarian Study at Boston Medical Center. Available at: http://www.bumc.bu.edu/Dept/Content.aspx?DepartmentID=361&PageID=5924. Accessed June 16 2008.

Chapter 5

Classification Controversies in Neurodegenerative Disease

The changes in cognitive function that occur with aging range in severity from mild to devastating. Cognition remains virtually intact in some individuals as they grow older, while others become dependent on caregivers. Traditionally, different diagnoses such as Alzheimer's disease and Lewy body dementia have been thought to present with different symptoms and arise through different disease processes. However, while many different forms of neurodegenerative disease are recognized, the lines that separate one from another are often unclear. For instance, symptoms such as motor impairment and memory loss may occur in many different types of neurodegenerative disease. Motor impairment similar to that seen in Parkinson's disease is not enough to rule out other diagnoses, especially when both motor and cognitive impairment are present. Other symptoms, such as hallucinations or agitation, are also not disease-specific. Since, with few exceptions, no diagnostic laboratory tests exist that can clearly indicate the presence, absence, or category of a neurodegenerative disease, diagnoses are usually based on clinical evaluation of the symptoms.

While many different forms of neurodegenerative disease are recognized, the lines that separate one from another are often unclear.

Brain pathology—often considered the hallmark of diagnosis—can also show marked overlap among the syndromes of age-related cognitive and motor impairment. The brains of individuals with different neurodegenerative disorders show characteristic cellular and tissue abnormalities upon histological examination. One of the earliest findings in autopsies of Alzheimer's patients was the presence of amyloid plaques and neurofibrillary tangles in the brain. Similarly, post-mortem examinations of patients with Parkinson's disease revealed the presence of abnormal protein aggregates known as Lewy bodies. Later work revealed that these pathological markers were aggregates of different types of protein: amyloid plaques consisted primarily of amyloid-beta, neurofibrillary tangles of tau, and Lewy bodies of alpha-synuclein. These early observations helped build the notion

In Japan, the pine tree is a symbol for longevity.

that neurodegenerative diseases are distinct in their causes and characteristics, each disorder with its own set of pathological features (see Table I). However, further research cast doubt on this assumption of "one disease, one pathology" as it became clear that the brains of individuals with one form of neurodegeneration could also have the pathological markers of another.[1] [2]

Nevertheless, while the notion of a discrete, clear correspondence between disease states and certain pathological markers has largely fallen by the wayside, it is still embodied in the current definitions of neurodegenerative diseases. Attempting to diagnose a neurodegenerative disease using contemporary diagnostic standards can be likened to trying to fit shoes of one size to a randomly selected group of individuals: for the majority of them, the shoes will be either too big or too small, and for only a fraction of the group will they fit perfectly. By the same token, due to the diversity of symptoms and pathologies that exist in the real world, the number of instances where the tissue diagnosis perfectly fits the clinical disease is rather small. Instead of fitting into a simplistic conventional framework, many patients display clinical findings that overlap or otherwise do not neatly fit into current diagnostic categories.

Problems with Dichotomous Definitions

When classifying neurodegenerative diseases, an initial question is "how much is enough?" When a patient first presents with abnormal neurological findings, symptoms may be mild and nonspecific and the course that the condition will take is often unclear: will the symptoms grow progressively worse, will they subside, or will they not change at all? The associated neuropathology is also unknown initially and, depending on the condition, may remain unknown or unrevealed until much later, perhaps at postmortem examination. In some neurodegenerative disorders, health and disease may be separated by shades of gray. Neurological changes build up gradually over time, and clinicians frequently ask how severe symptoms must be or how much pathology is necessary to apply a disease label.

A second problem relates to categorizing or naming the disease. When more than one possible diagnosis exists for a given set of symptoms or tissue pathologies, which one is appropriate? Neurodegenerative disorders sometimes defy rigid classification and subjective judgment is often unavoidable in the diagnosis of these conditions.

Despite the limitations of the current framework of neurodegenerative diseases, it at least offers a starting point for understanding this wide range of conditions. Table II is a brief overview of some of the currently recognized forms of neurodegeneration, following the one disease–one pathology framework

Condition	Pathological Markers	Main areas affected
Alzheimer's disease	Amyloid plaques, neurofibrillary tangles	Cerebral cortex, hippocampus, basal nucleus of Meynert
Lewy body dementia	Lewy bodies	Cerebral cortex, substantia nigra, basal nucleus of Meynert
Parkinson's disease	Lewy bodies	Substantia nigra, dorsal motor nucleus of the vagus, basal nucleus of Meynert
Vascular dementia	Vascular infarctions, atherosclerosis, and other markers of vascular disease	Cerebral cortex, hippocampus
Progressive supranuclear palsy	Neurofibrillary tangles	Cerebral cortex, basal ganglia, spinal cord, midbrain
Corticobasal degeneration	Ballooned neurons with tau inclusions	Cerebral cortex, basal ganglia
Multiple system atrophy	Alpha-synuclein inclusions	Hindbrain structures involved in balance and autonomic functions

Table I. Abridged list of neurodegenerative diseases, associated pathological markers, and main areas of the brain that are affected

More information on the pathological markers of neurodegenerative diseases can be found in chapter 3.

The one disease–one pathology framework naturally led to the investigation of the role of pathological markers in their respective disease processes. However, research has consistently shown that pathological markers do not always correlate well with clinical findings, and that some individuals with extensive neuropathology may retain relatively intact neurological function while others with less extensive pathology may be significantly impaired.[3-6] This relatively poor correlation has led some to question the value of relying too heavily on these markers for diagnostic purposes. Reflecting this uncertainty, pathologists often ask the clinician about the nature and extent of neurological impairment during life before labeling a neurodegenerative disease postmortem.

Mixed Pathologies May Be the Main Driver of Dementia

Although the correlation between the extent of single kinds of pathological markers and clinical symptoms is relatively poor, the presence of multiple kinds of pathology may be a much better predictor of the degree of cognitive impairment.[7] A recent community-based study that compared cognitive status with pathology found that subjects whose brains had the pathological markers of more than one disease type were by far the most likely to have shown signs of cognitive impairment during clinical evaluation.[8]

Table II. Syndromes of Motor and Cognitive Impairment: Conventional Definitions*

Syndrome	Definition	Basic Symptoms
Alzheimer's disease	Progressive neurodegenerative disorder typified by memory impairment with executive dysfunction, motor problems, and/or language difficulties.	• Personality changes • Cognitive impairments (declarative memory loss, difficulty with names) • Language difficulties • Motor difficulties • Delusions • Hallucinations
Lewy body dementia	Progressive neurodegenerative disease characterized by memory impairments, fluctuations in cognitive function, persistent visual hallucinations, and Parkinsonian motor symptoms.	• Cognitive impairments (declarative memory loss, difficulty with names, etc.) • Repeated falls • Syncope • Delusions • Detailed hallucinations • Depression • Anxiety • Rigidity • Mask-like face
Parkinson's disease	Progressive neurodegenerative disease that impairs ability to execute conscious physical movement in addition to other motor functions. Mood disturbances may occur as well.	• Slowing of voluntary movements • Muscle rigidity • Resting tremor • Difficulty speaking and swallowing • Gait and postural disturbances • Fatigue • Tiny handwriting
Vascular dementia	Cognitive impairment resulting from vascular disease in the brain, which can be either focal or diffuse. The severity of cognitive decline depends on the nature and extent of vascular involvement.	• Cognitive deficits associated with stroke • Other symptoms of Alzheimer's disease
Multiple system atrophy	Progressive degeneration of the autonomic nervous system involving motor impairment.	• Low blood pressure when standing up • Abnormal breathing during sleep • Difficulty urinating • Dry mouth and skin • Abnormal sweating

**This list is far from exhaustive. The descriptions are simplifications intended only to provide background information.*

Syndrome	Definition	Basic Symptoms
Frontotemporal dementia	Neurodegenerative disease featuring cortical atrophy with progressive behavioral changes and language dysfunction. Motor and cognitive impairment may be present as well, although some apparent cognitive deficits may be due to inability to focus on tests.	• Altered personality and social conduct • Apathy • Blunting of emotions • Disinhibition • Impaired planning • Impaired memory, attention, perception, and/or language • Parkinsonian motor symptoms
Progressive supranuclear palsy	Rare neurodegenerative disorder characterized by gait and balance disturbances as well as dementia. Frequently misdiagnosed as Alzheimer's disease or Parkinson's disease.	• Loss of balance • Difficulty moving eyes • Slowing of movement • Slurred speech • Personality changes
Corticobasal degeneration	Rare form of neurodegeneration that may involve asymmetrical motor impairment as well as dementia.	• Language impairment • Abnormal posture • Muscle twitches • Alien hand syndrome
Amyotrophic lateral sclerosis	Progressive degenerative disorder affecting motor neurons in many parts of the brain. Loss of motor neurons results in progressive loss of voluntary muscle movement, which in turn leads to muscle atrophy. Motor impairment may eventually affect respiratory systems. Cognitive function usually remains intact.	• Progressive motor impairment • Impaired speech • Muscle twitching and cramping • Abnormal posture
Multiple sclerosis	Demyelinating autoimmune disorder resulting in physical disability that may be progressive. Severity of disability ranges widely between individuals.	• Motor abnormalities typically following a temporal pattern of remission and relapse • Muscle weakness • Coordination problems • Difficulty speaking and swallowing • Impaired bladder function • Depression • Fatigue • Memory impairment

While the presence of amyloid plaques was the greatest single predictor of cognitive impairment, plaques were also commonly found in cognitively healthy subjects. Of the subjects that fulfilled the neuropathological criteria for Alzheimer's disease, fewer than half actually had cognitive impairment. In contrast, mixed pathologies such as amyloid plaques with Lewy bodies or vascular infarctions, were rare in persons without dementia. The authors concluded that having multiple disease pathologies conferred a nearly threefold increased risk of dementia compared to having only one type of pathology. Although all studies of the correspondence between clinical symptoms and neuropathology are limited by some degree of subjectivity inherent in the current protocols for disease classification, other community-based studies have produced similar findings.[9] [10]

Although the notion of one disease, one pathology has long influenced thinking about dementia, neuroscientists and clinicians now increasingly address the possibility of a major role for multiple pathologies and the disease processes that drive them. The number of published studies on this topic is still relatively small, and more work is needed to elucidate the contributions of multiple brain pathologies to dementia, particularly with respect to how they may interact. However, if the presence of more than one type of pathology is indeed the greatest predictor of cognitive impairment, there could be a paradigm shift in how we think about dementia.

Traditionally, loss of cognitive function with old age has been viewed fatalistically. However, to the degree that mixed pathology is an important antecedent, particularly when involving vascular disease, a variety of proven preventive measures become relevant and hold promise. We know that the likelihood of developing atherosclerotic vascular disease can be reduced by attention to diet, exercise, smoking cessation, and treatment of hypertension and hyperlipidemia. Taking these steps to improve cardiovascular health is likely to reduce risks of cognitive impairment. Furthermore, interventions that mitigate oxidative stress and inflammation (see chapter 6) might also prevent or slow the progression of neurodegenerative conditions like Alzheimer's disease, Parkinson's disease, or cardiovascular disease in which those processes play key roles. Thus, lifestyle changes and a variety of public policy decisions could potentially play an important role in reducing the burden of neurodegenerative disease over the coming decades.

Continuum of Age-Associated Cognitive Impairment

Lifestyle changes and a variety of public policy decisions could potentially play an important role in reducing the burden of neurodegenerative disease over the coming decades.

Adherence to traditional disease categories and dichotomous definitions of disease (which label individuals as either "sick" or "not sick") may have contributed to current challenges in diagnosing and studying neurodegenerative conditions. For example, disease misclassification in epidemiologic studies adds to the difficulties in consistently identifying risk factors for specific conditions.

Current uncertainties have inspired some neuroscientists and clinicians to suggest that neurodegenerative diseases characterized by abnormal protein deposits should be viewed as existing along a continuum of symptoms and pathologies rather than as discrete entities.[11] [12] Such a spectrum of neurological impairment could better represent the heterogeneity within diagnostic categories as well as the many pathways by which different individuals can arrive at the same condition.

It is worth noting that the pathological markers themselves are not necessarily the cause of the underlying disease and clinical symptoms. Instead they may actually be a response to other antecedent disease processes, although it is entirely possible that at some later time, the pathological markers may actually begin to contribute to disease progression in a positive feedback loop. A more detailed look at the pathology associated with diseases represented along this spectrum reveals not only abnormal protein deposits but also widespread evidence of an underlying chronic inflammatory reaction characterized by activated microglia and up-regulation of various inflammatory markers. This suggests that a closer look at the origins of oxidative stress and inflammation more generally may help to identify environmental factors that increase susceptibility to neurodegenerative diseases. We turn now to a more detailed discussion of these processes at the tissue, cellular, and subcellular levels before addressing Alzheimer's disease and Parkinson's disease directly.

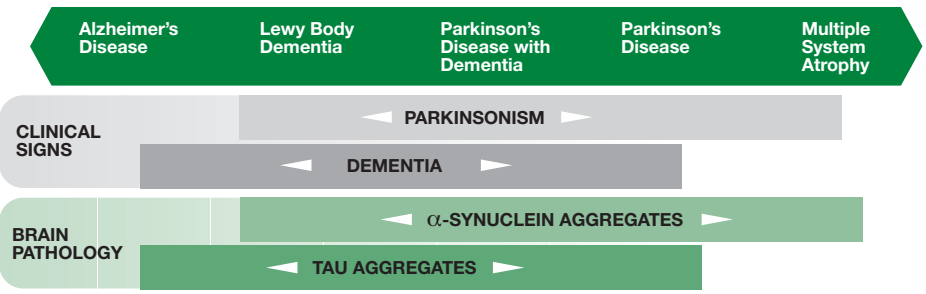


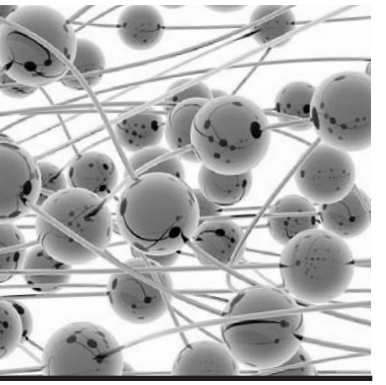
Figure 1: A continuum of neurodegenerative diseases characterized by abnormal protein deposition[13]

Endnotes

1. Schneider JA, Arvanitakis Z, Bang W, Bennett DA. Mixed brain pathologies account for most dementia cases in community-dwelling older persons. Neurology. 2007;69:2197-2204.
2. Langa KM, Foster NL, Larson EB. Mixed dementia: emerging concepts and therapeutic implications. JAMA. 2004; 292:2901-2908.
3. Neuropathology Group of the Medical Research Council Cognitive Function and Aging Study (MRC CFAS). Pathologic correlates of late onset dementia in a multicentre, community based population in England and Wales. Lancet. 2001; 357:169-175.
4. Prohovnik I, Perl DP, Davis KL, Libow L, Lesser G, Hartounian V. Dissociation of neuropathology from severity of dementia in late-onset Alzheimer disease. Neurology. 2006;66:49-55.
5. Riley KP et al. Alzheimer's neurofibrillary pathology and spectrum of cognitive function: findings from the nun study. Ann Neurol 2002;51:567-577.
6. Schneider JA, Arvanitakis Z, Bang W, Bennett DA. 2007.
7. Bennett DA, Schneider JA, Arvanitakis Z, et al. Neuropathology of older persons without cognitive impairment from two community-based studies. Neurology. 2006; 66:1837-1844.
8. Schneider JA, Arvanitakis Z, Bang W, Bennett DA. 2007.
9. Neuropathology Group. 2001.
10. White L, Small BJ, Petrovitch H, et al. Recent clinical-pathologic research on the causes of dementia in late life: update from the Honolulu-Asia aging study. J Geriatric Psych Neurol. 2005;18:224-227.
11. Neuropathology Group. 2001.
12. Tanner C. Presentation at International Neurotoxicology Conference XXIV, San Antonio, TX. Nov 2007.
13. Modified from: Tanner C. Presentation at International Neurotoxicology Conference XXIV, San Antonio, TX. Nov 2007. Used with permission.

Chapter 6

Underlying Dimensions of Neurodegenerative Disease



An Exploding Field Of Research

Research on the nervous system—its development, function, and degeneration—encompasses a vast and rapidly expanding universe of information. Revolutionary advances are taking place in a variety of relevant fields, from genetics to brain imaging, immunology, molecular chemistry, information processing, physical chemistry and more. Comprehending the evidence from so broad a field is a daunting challenge. As summarized more than a decade ago by G. Reid Lyon, a noted neurobiologist and former branch Chief at the National Institutes of Health, "[T]he literature relevant to these domains is so voluminous that the important converging trends in the data are sometimes difficult to identify and apply… . This difficulty is exacerbated by the application of divergent theories, methodologies, and vocabularies."[1]

This chapter attempts to make some of this vast body of information more accessible to a broader audience. We also hope to help bridge some of the communication gaps within the highly subspecialized scientific community. To do so, we have provided considerable technical detail, since many scientists outside the narrow domains of these subjects will be unfamiliar with them. Though much of the technical information is contained in an appendix on the web site for this report, some of the hard science remains in the chapter—particularly in diagrams, footnotes, and some of the sidebars. We encourage readers who do not want to navigate through the technical details to simply bypass these sections since the take-home message is provided in adjacent portions of the chapter.

Amethyst is a symbol of health and healing. It was believed to ward off drunkeness by the Ancient Greeks.

Environmental factors... interact with the immune system and metabolism to profoundly influence health and disease risk.

The chapter discusses selected topics essential to understanding the nervous system and neurodegenerative disease. These subjects span the fields of chemistry, biology, nutrition, and clinical medicine. This discussion will lay the groundwork for chapters 7 and 8, which examine environmental factors as they relate to neurodegenerative disease. This chapter also provides a reference for terms for which some readers may want a deeper understanding. The topics in this chapter, which appear throughout the scientific literature on health and disease, are important for understanding environmental factors in chronic disease of the brain and other organ systems. As we'll discuss, they contribute to a unifying framework for understanding current evidence about the causes of neurodegenerative disease.

In short, a complex picture emerges in which environmental factors—including nutrition, toxic exposures, exercise, and social conditions among others—interact with the immune system and metabolism to profoundly influence health and disease risk. Inflammation and oxidative stress, which are central to these processes, are turning out to be key themes in neurodegenerative disease—just as they are in a larger complex of chronic diseases including cardiovascular disease and diabetes. The emerging science underscores the need to expand the health paradigm to include—as key determinants of health—the systems that support good nutrition, exercise, a clean environment, and the social fabric of communities. Therein lies a monumental opportunity for prevention.

Part 1: The Key Role of Inflammation and Oxidative Stress

This chapter focuses heavily on oxidative stress and inflammation for several reasons. These two interrelated processes are increasingly accepted as integral to the development and progression of many chronic diseases. Inflammation and oxidative stress figure prominently among the various pathological features and processes shared by neurodegenerative diseases (despite varying clinical manifestations, as discussed in chapters 5, 7, and 8). Most neuroscientists agree that inflammation and oxidative stress are typically key components of the final common pathways leading to brain cell death and the decline of brain function. A variety of other processes are also involved, as will be discussed, which are all interrelated. Oxidative stress is especially important in the brain—among all organ systems—because of unique conditions that make the brain vulnerable: high oxygen consumption (the ultimate source of oxidative

stress), relatively limited supply of antioxidants, and high content of polyunsaturated lipids, the macromolecules most susceptible to oxidative damage.

Finally, inflammation and oxidative stress are of particular interest because their links to modifiable real world conditions—including nutrition, exercise, air pollution, and other chemical exposures—have been well documented. This provides a compelling basis for a variety of precautionary interventions to prevent or at least delay the onset or progression of neurodegenerative diseases.

Inflammation: The Immune System at Work

Inflammation is the process by which the immune system defends the host from organisms or material perceived as foreign and potentially threatening. As far back as the first century AD, the Roman encyclopedist Celsus identified inflammation as a constellation of four physical signs: Heat, pain, redness, and swelling, or in classical medical language, "Calor, dolor, rubor, and tumor." These signs are readily visible, for example, in the inflammation that accompanies an infected wound or traumatized tissue. They reflect the actions of various cellular and chemical mediators that are part of the immune response.[2] The characteristic signs of inflammation can also occur in the absence of infection or trauma, as in the case of rheumatoid arthritis, asthma, or inflammatory bowel disease. In each of these diseases evidence of an inflamed organ system is apparent, at least indirectly—namely red, hot joints in rheumatoid arthritis, purulent sputum from inflamed lungs in asthma, and bloody, purulent diarrhea from an irritated gastrointestinal tract in inflammatory bowel disease.

Unlike classic inflammation, however, which was visible to the naked eye, the inflammation of chronic disease is hidden from view.

Inflammation is now emerging as a unifying theme in the chronic diseases of western society.[3-8] (See sidebar, *A Western Disease Cluster)* Unlike classic inflammation, however, which was visible to the naked eye, the inflammation of chronic disease is hidden from view, and apparent only with blood tests or microscopic analysis of pathological specimens. For example, in atherosclerosis, the major cause of heart attacks and strokes, inflammatory markers can be found circulating in the blood and embedded—along with activated inflammatory cells—in atherosclerotic plaques. (Plaques are areas of focal swelling in the blood vessel wall—where various cells, lipid and debris accumulate—which can obstruct circulation.)

The inflammatory nature of atherosclerosis was established in a landmark 1999 article characterizing it as "a series of highly specific cellular and molecular responses that can be best described, in aggregate, as an inflammatory disease."[18] Another key study in 2003

found that C-reactive protein, an inflammatory marker in the serum, was a stronger predictor of future cardiovascular disease than LDL ("bad") cholesterol. This suggested that the inflammatory model of cardiovascular disease is at least as accurate and useful as the conventional lipid model.[19] [b] As we'll see, lipids and inflammation are closely related, so the two models of cardiovascular disease may best be viewed as complementary.

Similarly, inflammation is implicated in type 1 diabetes, which is widely acknowledged as an autoimmune disease characterized by destruction of the insulin-producing beta cells in the pancreatic islets. [20] [21] A growing body of research over the past two decades indicates that a variety of other chronic diseases have important inflammatory components, including type 2 diabetes,[22] [23] metabolic syndrome,[24] [25] obesity,[26] [27] neurodegeneration,[28] depression,[29] [30] [31] and osteoporosis.[32]

Affected individuals frequently carry telltale signs of inflammation in their blood or in the organ system involved. These telltale signs, referred to as biomarkers or inflammatory markers, are found in all people, but are frequently at higher levels in people with chronic inflammatory diseases. The inflammatory markers include substances such as C-reactive protein, tumor necrosis factor (TNF), prostaglandin

[b] *While the lipid model relies primarily on the concept of lipid accumulation, analogous to "clogged pipes", the inflammatory model also incorporates additional mechanisms—including plaque instability and rupture, and platelet aggregation.*

A "Western Disease Cluster"

It is commonly observed that a number of chronic illnesses endemic to the modern Western world tend to occur together both within societies and within individuals.[9] [10] [11] This cluster of chronic diseases, referred to in this report as the Western disease cluster, includes diabetes, obesity, hypertension (and other manifestations of cardiovascular disease), and dyslipidemia (abnormalities in the quantity or quality of blood lipids). There is growing evidence to suggest that dementia—including Alzheimer's disease—may be a part of this cluster as well.

Substantial evidence supports a cluster concept for this group of metabolic and vascular-related disorders. [12-15] One line of evidence is provided by the fact that many of these illnesses are risk factors for each other.

The concept of a cluster is further supported by the existence of a specific disorder, the metabolic syndrome, consisting of concurrent early features of the cluster diseases: borderline elevations of blood sugar and blood pressure, elevated triglycerides and/or low HDL cholesterol, and obesity.[a] Individuals with metabolic syndrome have markedly increased risks for developing type II diabetes and coronary disease.[16]

The public health significance of metabolic syndrome is reflected in a disturbingly high prevalence of over 40 percent among adults aged 60 years and older, and 24 percent among the population at large.[17] Each of the disease components of metabolic syndrome, when occurring during midlife, also constitutes a risk factor for dementia/cognitive decline. Growing evidence also implicates the metabolic syndrome itself as an important risk factor for dementia.

And finally, the cluster concept is supported by evidence of common mechanisms including immune activation, vascular dysfunction and inflammation, and insulin resistance/hyperinsulinemia as described in this chapter. These mechanisms are recognized as playing key roles in dementia/cognitive decline as well as in diabetes, cardiovascular disease/hypertension, metabolic syndrome, obesity, and dyslipidemia.

[a] *Obesity in metabolic syndrome is usually defined by increased waist circumference.*

E2 (PGE2), and others. Usually biomarkers are more than passive bystanders—they are active agents in the inflammatory process. Inflammatory markers are signs of immune system activation, a process emerging as central to the etiology of chronic diseases in the developed world. These markers and their relationship to the immune system are discussed in several sections below.

Like inflammation, oxidative stress also increases in aging and especially in neurodegenerative diseases like Alzheimer's and Parkinson's disease.

Inflammation in the Brain

In the brain, inflammation is mediated largely by glial cells, the support cells of the nervous system. (See chapter 3.) Glial cells include astrocytes, which support neuronal metabolism, oligodendrocytes which produce myelin insulation for nerve cells (allowing more efficient conduction of nerve impulses), and microglia, which serve as a kind of immune system. Glial cell activation is a key feature of brain inflammation. When activated, microglia produce inflammatory mediators that activate more cells to produce additional inflammatory mediators. These mediators can thus create positive feedback loops, thereby amplifying inflammation.

Brain inflammation, including increased microglia and astrocyte activation, generally increases as part of the aging process. Brain inflammation is also a key feature of neurodegenerative diseases, including Alzheimer's and Parkinson's. In Alzheimer's disease, inflammation and oxidative damage are found from the earliest stages of the disease, through the formation of amyloid plaques, and the widespread death of nerve cells. [c] [33]

Oxidative Stress

Inflammation is closely related to the process of oxidative stress. Like inflammation, oxidative stress also increases in aging and especially in neurodegenerative diseases[34] like Alzheimer's[35] and Parkinson's disease.

Oxidative stress is a metabolic state in which excessive levels of highly reactive, unstable oxygen compounds are present in the body, an organ system, or tissue. These unstable oxygen compounds are referred to

[c] *The inflammatory mediators produced by microglia—including interleukin-1 (IL-1), interleukin-6 (IL-6), and tumor necrosis factor α(TNFα)—increase the expression of amyloid precursor protein from which amyloid-beta is derived. IL-1 and IL-6 are typically found surrounding the amyloid plaques as well. In another example of a pathologic positive feedback loop, amyloid-beta peptides stimulate the production of IL-1α, IL-6 and TNFα—mediators that promote amyloid-beta production in the first place.*

Unstable oxygen compounds are normally held in check by the cell's antioxidant systems.

as oxygen radicals, free radicals, or "reactive oxygen species" (ROS). ROS are normally held in check by the cell's antioxidant systems. Oxidative stress occurs when these defenses are overwhelmed—due to either increased ROS or a deficiency of antioxidant mechanisms.[36] [37] In either case, damage results. ROS may be produced within the cell (endogenously), or may come from outside the cell (exogenously).

Exogenous sources of oxidative stress include air pollution; tobacco smoke; many different industrial chemicals including pesticides, solvents, bisphenol A, alkylphenols, type-2 alkenes (see chapter 8), among others; metals; polycyclic aromatic hydrocarbons, PCBs, dioxin, and other pollutants; radiation, anesthetics and a high-oxygen environment.[38]

Endogenous ROS are continuously formed under normal conditions as a byproduct of aerobic metabolism, the oxidative reactions that burn fuel to produce the cell's energy. In fact, about 2–5 percent of all oxygen used by a cell is converted into ROS.[39] This takes place primarily in mitochondria, the major site of oxygen utilization in the cell, where fuel is burned and energy is produced.[40] [41] [d]

Outside of the mitochondria, the most important site of ROS production is in immune cells when they are activated in an "oxidative burst." This occurs when phagocytic cells (literally "eating" cells) are activated as part of the immune response, in which these cells ingest or otherwise damage microorganisms such as bacteria, viruses,[42] or other material perceived as pathogenic.

ROS are highly reactive, chemically unstable, and damaging to the tissues they come in contact with—including the nucleic acids, lipids, and proteins that are essential building blocks of biological tissues.

Oxidative Stress in the Brain [e] [43] [44]

As mentioned above, the brain is particularly susceptible to oxidative stress because it has a relative lack of antioxidant systems,

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[d] *Within the mitochondria, ROS are continuously produced by oxidases and the electron transport chain associated with oxidative phosphorylation. Other reactions producing ROS include the actions of cyclooxygenases, lipoxygenases, dehydrogenases and peroxidases. The sites where these reactions take place include virtually all components of the cell, including the plasma membrane, mitochondria, lysosomes, peroxisomes, nucleus, endoplasmic reticulum and cytoplasm.*

[e] *Oxidative stress and inflammation are among several mechanisms that interact in complex ways to contribute to neuron loss. Other mechanisms include excessive stimulation of neurons (excitotoxicity), dysfunction of critical proteins, dysregulation of gene expression, mitochondrial dysfunction, abnormal calcium homeostasis, altered phosphorylation, abnormal cytoskeletal organization, increased extracellular matrix turnover, altered proteases/inhibitors, cell membrane malfunction, misfolding of proteins, decreased blood supply, and compromised stress responses. As we will see, these processes are interrelated. For example, misfolded proteins, compromised stress responses, and mitochondrial dysfunction contribute to oxidative stress and inflammation. These processes are in general also affected by aging.*

an abundance of readily oxidizable fatty acids, and high oxygen utilization leading to increased production of ROS.[45] [46] In addition, the brain contains relatively high levels of transition metals[47] including iron and copper. Normally these metals are carefully controlled in the brain. When these controls fail, transition metals can increase oxidative stress by catalyzing the production of ROS directly[48] or by binding amyloid-beta and catalyzing the production of ROS.[49-51]

The buildup of oxidative damage, particularly within mitochondria—the powerhouse of the cell—is thought to be key to the process of aging. Oxidative damage to mitochondria is also believed to be an important underlying problem in Alzheimer's disease. This theory is supported by the observed reduction in brain metabolism that occurs in Alzheimer's patients, indicating reduced mitochondrial activity. Reduced brain metabolism has been reported to precede the development of abnormalities in neuropsychological testing, suggesting impaired brain metabolism plays a causal role in the web of Alzheimer's pathogenesis.[52] Oxidative damage to mitochondria also plays a role in Parkinson's disease. Some of the toxicants damaging dopamine-producing cells in the substantia nigra have been shown to operate by injuring mitochondria. These findings are part of a growing body of evidence that suggests that oxidative stress is in fact an important pathologic mechanism in neurodegenerative disease, and that it begins early in the disease process.[53-57]

The buildup of oxidative damage, particularly within mitochondria—the powerhouse of the cell—is thought to be key to the process of aging.

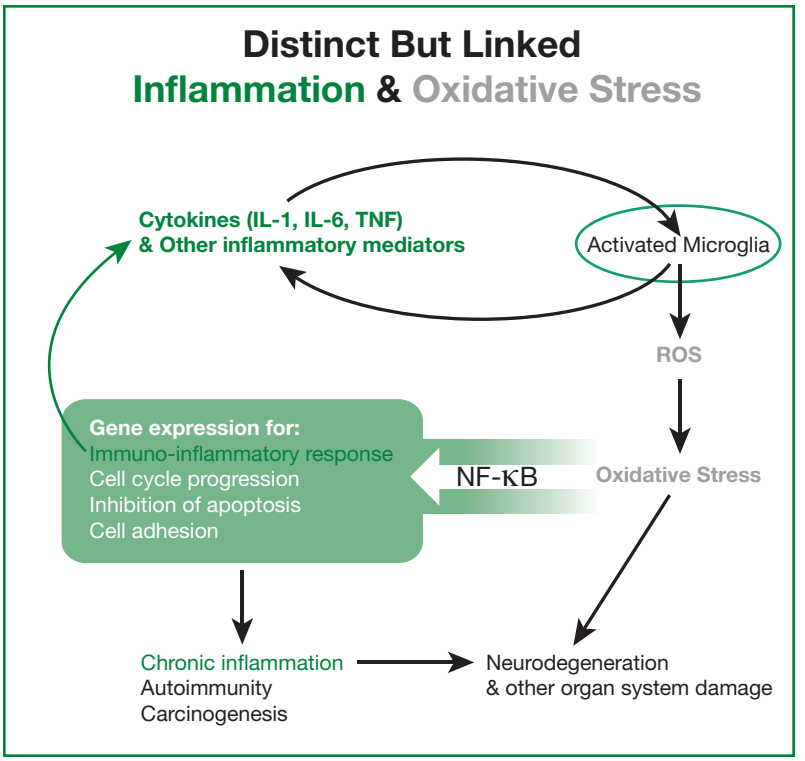
Oxidative Stress and Inflammation: Distinct but Linked

While oxidative stress and inflammation consist of distinct biochemical cascades, the processes are closely intertwined and generally function in parallel, particularly in the brain, which is especially prone to oxidative stress. When evidence of oxidative stress is found in brain specimens (i.e. ROS and the markers of their damage), evidence of inflammation (cytokines and other inflammatory mediators, activated immune cells, etc.) is also generally present.

While much remains to be learned about oxidative stress and inflammation—and their interactions—at least two major points of convergence are known which explain their tendency to occur together and reinforce each other. These points of intersection are shown in the accompanying diagram.

1. The inflammatory response can trigger or increase oxidative stress. Activated microglia (and outside of the brain, similar immune cells such as macrophages, monocytes and leukocytes) produce ROS as part of their arsenal of defenses against pathogens (or their markers). If the ROS overwhelm the cell's antioxidant capacity, oxidative stress results with consequent damage to essential molecules and tissues. [58]

2. Oxidative stress can trigger or increase inflammation through the activation of nuclear factor kappa B (NFkB), which is known to be sensitive to oxidative stress.[59] NFkB is a "transcription factor," that is, it controls the expression of various genes, including a variety of genes involved in the inflammatory response. NFkB is generally associated with chronic inflammation and has also been linked to several cancers.[60-62] Available evidence indicates that NFkB is key to the pervasive effects of oxidative stress.



Similarly, a variety of evidence suggests that amyloid-beta, a key factor in Alzheimer's disease, interacts in complex ways with inflammation and oxidative stress. While there is evidence of complex interactions—with amyloid-beta causing ROS/inflammation,[f 63 64] and ROS/inflammation causing amyloid-beta production[g 65 66]—evidence increasingly suggests that oxidative stress and inflammation commonly initiate this process.[67-70]

The Innate Immune System

Many of the biomarkers relevant to neurodegeneration are part of the innate immune system, one of two major subdivisions of the immune system. A growing body of biomarker data (and other evidence) increasingly points to the importance of innate immune activation in neurodegeneration as well other chronic diseases of the Western world—namely diabetes, metabolic syndrome, obesity, and cardiovascular disease. Thus, understanding innate immunity is especially important to understanding chronic inflammatory disease.

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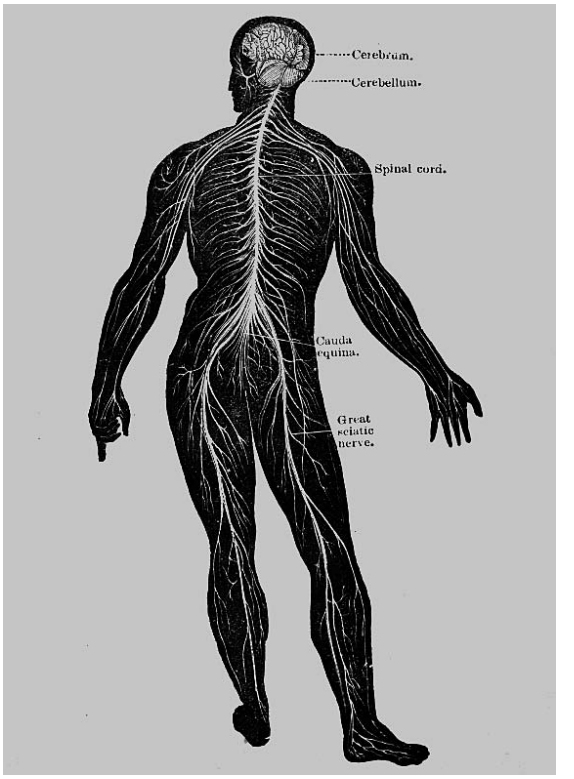
[f] *Amyloid-beta, for example, stimulates neuronal production of hydrogen peroxide and other ROS. Amyloid-beta is also known to bind copper which is itself a catalyst for hydrogen peroxide formation. In addition, amyloid-beta fibrils, found in the senile plaques that identify Alzheimer's disease, activate microglia, which are typically found along with reactive astrocytes surrounding amyloid plaques.*

[g] *For example, inflammatory mediators (interleukin-1, interleukin-6, tumor necrosis factor), found in the areas surrounding amyloid plaques, have also been found to stimulate the production of the amyloid precursor protein (from which amyloid-beta is derived). Oxidative stress has also been shown to induce the production of amyloid-beta protein.*

The other major component of the immune system—in addition to the innate immune system—is the adaptive immune system. Both the innate and adaptive systems enable the organism to defend itself against invaders such as bacteria, viruses, and fungi. Humans possess both systems, which are closely interconnected in the functioning of the immune system.[71] Nonetheless, there are major differences between the two.



While innate immunity was established very early in evolution and is possessed by virtually all animal species, adaptive immunity is possessed only by animals at the evolutionary level of jawed-vertebrates. The innate immune system reacts immediately to molecular patterns associated with pathogens in general—so called "pathogen-associated molecular patterns" or PAMPs. PAMPs are recognized by pattern recognition receptors, also called Toll-like receptors (TLR), which then induce inflammatory and immune responses. No prior exposure is needed to mount an innate immune response.

In contrast, the adaptive immune system responds slowly, over several days, generating a response to particular, narrowly defined chemical patterns unique to a particular infectious agent or other pathogen. This response produces specific antibodies that mark the organism (or related material) for destruction. Prior exposures are remembered by the adaptive immune system, which enables a quicker response upon re-exposure.[72]

Understanding innate immunity is especially important to understanding chronic inflammatory disease.

A Key Link Between Fatty Acids and the Innate Immune System: The Critical Role of Saturated Fat in Lipopolysaccharide

Perhaps the best-known PAMP is the material derived from the cell wall of some common bacteria, called lipopolysaccharide (LPS). LPS, also known as endotoxin, is a key substance responsible for the activation of the innate immune system by bacterial infection. When full blown, the inflammatory response caused by LPS/endotoxin can include shock, multi-organ failure, and death.[73]

FOOD *for* THOUGHT

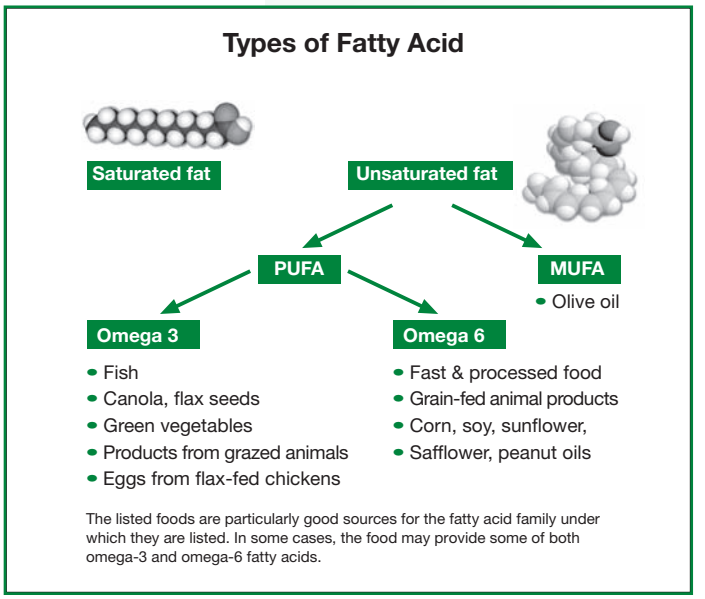
Introduction to Fatty Acids, Key Players in Immune Function

Fatty acids are the major lipids in the diet. Fatty acids and their derivatives provide structural building blocks for cell membranes. Fatty acids are also major components of triglycerides, a form of fat used to store energy in adipose (fatty) tissue. Fatty acids are found in all tissues and are carried in the blood in the form of lipoproteins or as free fatty acids. Derivatives of long chain omega-3 fatty acids in particular are highly concentrated in the brain. Increasingly fatty acids are recognized as having biologically active properties including the regulation of genes involved in inflammation and metabolism. [83]

Where's the fat?

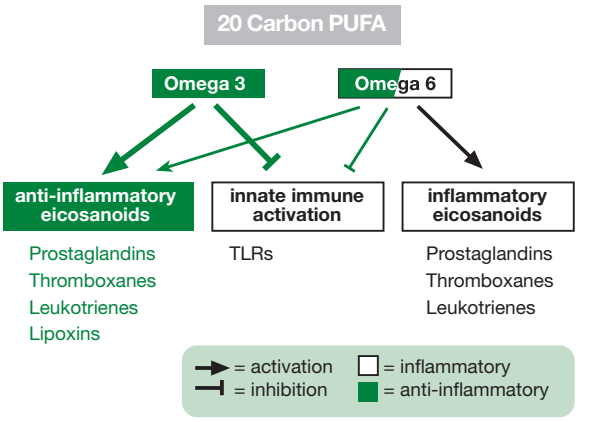
cell membranes
fat tissue
blood
brain

Fatty acids are composed of carbon chains typically between 12 and 24 carbons in length, surrounded by hydrogen atoms, with an acid group attached at one end of the chain. Saturated fats are geometrically straight due to the similarity of the single bonds between each of the carbons in the chain. Unsaturated fatty acids have one or more double bonds between carbon atoms, causing a kink in the chain at each double bond. The kinks prevent the unsaturated fat molecules from tightly aligning with each other, causing unsaturated fats to be liquid at room temperature, where as saturated fats are solid. Monounsaturated fatty acids (MUFAs)—which include the major fatty acid in olive oil, oleic acid—have one double bond. Polyunsaturated fatty acids (PUFAs) have more than one double bond and can be divided into the omega-3 and omega-6 families. The omega-3 fatty acids all share a double bond at the third carbon from the methyl end of the chain. Omega-6 fatty acids have a double bond at the sixth carbon position from the methyl end of the chain, and a single bond at the third carbon. Omega-3 fatty acids are found in the chloroplasts of green plants.[84] Thus the sources of omega-3 fatty acids in the human diet include green plants and foods derived from animals with green plants or algae in their food chains—including fish and to a lesser extent, the products of pasture-fed animals. Omega-6 fatty acids are found in grains and are concentrated in vegetable oils and the products (especially fast foods) that incorporate them. Saturated fats are increased in fatty meats from confined, grain-fed animals, which provide most animal-based foods in the US. (Food products from animals grazed on green



pasture have increased levels of omega-3 fatty acids.[85]) Other sources of saturated fat include baked goods, cheese, milk, margarine and butter.[86]

Fatty Acids, Eicosanoids and Innate Immunity



This diagram illustrates two important ways that omega-3 and omega-6 fatty acids interact with the immune system. The net result is that omega-6 fatty acids can have both inflammatory and anti-inflammatory effects, while omega-3 fatty acids have predominantly anti-inflammatory effects. Omega-6s have an inflammatory effect as the sole substrate for highly inflammatory eicosanoids.[87] Omega-6s can also have anti-inflammatory effects—by giving rise to less prominent anti-inflammatory eicosanoids[h] [88] and by inhibiting innate immune activation by saturated fat through the Toll-like receptor. (See Part 2 of this chapter.) Omega-3 fatty acids, on the other hand, give rise to relatively anti-inflammatory eicosanoids and are much more potent inhibitors of innate immune activation through the Toll-like receptor.[89]

Selected properties of omega-3, omega-6, and saturated fats, as discussed in this report, are listed below. Health effects of the various types of fatty acids are discussed in chapter 7.

Properties of Fatty Acids

	Omega-3	Omega-6	Saturated
Food system properties	• Perishable • Short shelf life	• Durable • Processed foods • Long shelf-life	• Increased in factory farmed animal products
Immune properties	anti-inflammatory	inflammatory & anti-inflammatory	inflammatory
Evolutionary context	recent marked decline	recent marked increase	recent marked increase

[h] *Omega-6 linoleic acid (LA) is elongated to arachidonic acid (AA), the substrate for inflammatory eicosanoids. However, an intermediate between LA and AA, dihomo-GLA (DGLA) itself can give rise to the relatively anti-inflammatory 1-series prostaglandins. Thus LA can give rise to both inflammatory and anti-inflammatory prostaglandins.*

Saturated fat itself plays a critical role in... stimulating innate immunity.

The portion of LPS that causes most biological activity, lipid A, contains saturated fat.[i] If the saturated fat is removed from LPS, the LPS is no longer immunologically active, causing a complete loss of endotoxic activity. [74] Further, lipid A without saturated fat functions as an antagonist to native lipid A. Thus, saturated fat has been shown to be essential for the potent endotoxic, immunologic effect of LPS. [75-77]

A growing body of evidence suggests that saturated fat itself plays a critical role in activating the Toll-like receptors and stimulating innate immunity—even without LPS.[78-80] This provides an important mechanism that may be key to the observed association between diets high in saturated fat and Western chronic diseases—cardiovascular disease, insulin resistance/diabetes and others. It should be noted that elevated levels of fatty acids in the blood are associated not only with obesity and dietary ingestion, but may also reflect endogenous lipid formation, which is activated in the state of insulin resistance. The interaction of Toll-like receptors and fatty acids, and the implications for chronic Western diseases (including Alzheimer's) is discussed in the sections on Insulin and TLR Signaling below.

While LPS exposure has largely been associated with bacterial infection, recent evidence from human and animal studies shows that LPS exposure can occur in the absence of infection via absorption from the intestinal tract into the blood. The degree of absorption of LPS from the gastrointestinal tract depends on the bacterial composition of the intestine and, importantly, can be modulated by diet. In 201 apparently healthy men, LPS levels in blood plasma were higher in those who reported a higher level of dietary fat and total energy intake.[81] All fat types, saturated, monounsaturated, and polyunsaturated, showed this trend. In a study in mice, LPS levels in blood increased with dietary fat and could be modified by the use of broad spectrum oral antibiotics, which altered the bacterial flora in the intestine.[82] These observations, among others, underscore the important and complex interconnections between diet, the intestine, and the immune system.

[i] *Specifically, lipid A contains the saturated fats hydroxymyristate, laurate, and myristate that are acylated onto a glucosamine moiety.*

Part 2: Cell Signaling

The inflammatory mediators referred to in the previous sections can be seen as part of a larger category of cellular communication—generally referred to as cell signaling. Cell signaling, simply put, refers to communication and crosstalk among and within cells. This communication collectively informs an organism of conditions in its external or internal environment, allowing a response to occur. Hormones, neurotransmitters, and growth factors are examples of signaling among cells. Within cells, the basic processes of cellular function, such as metabolism or gene expression, are also comprised of cell signaling.

Cell signaling cascades... link fatty acids and other dietary factors, innate immunity, insulin resistance, and diabetes-associated diseases.

Recent exciting developments in this field have revealed a complex of cell signaling cascades that link fatty acids and other dietary factors, innate immunity, insulin resistance, and diabetes-associated diseases—including vascular disease (in the heart, brain, and peripheral arteries), hypertriglyceridemia and Alzheimer's. Thus, common cell signaling pathways appear to provide compelling mechanistic explanations for observed patterns of disease—and their association with chronic immune activation and Western nutrition. Cell signaling pathways also integrate inputs from genetic and other environmental factors—including toxicants, exercise, obesity, psychosocial stress and health conditions—into the complex web of conditions influencing health and disease risk.

Signaling cascades are sequences of signaling molecules in which the activation of one kind of molecule triggers activation of molecules downstream. Signal initiation often relies on protein receptors located in the cell membrane. Cascades translate signals from outside the cell into signals and ultimately actions within the cell. They are thus a critical interface between the outside world and the internal domain of the cell.[i] All of these signals are intimately involved in the vast web of basic cellular function.

Here we introduce two signaling cascades, the insulin cascade and the Toll-like receptor cascade, which are emerging as central in nutrition, metabolism, chronic immune activation, and vascular function.

[i] *Some signaling molecules—such as steroid hormones—work through nuclear receptors rather than cell surface receptors.*

The Insulin Cascade

Insulin is a powerful metabolic hormone affecting virtually every tissue in the body.[90] Key insulin actions include facilitating the uptake of glucose from the blood, synthesis of glycogen (a complex of many glucose molecules stored in muscle and the liver), production of nitric oxide by endothelial cells lining the inner blood vessel (allowing blood vessels to dilate, keeping them agile and healthy), and the inhibition of triglyceride synthesis (suppressing levels of serum triglyceride as well as VLDL,[k] a lipoprotein that carries much of the triglyceride in the bloodstream). The insulin cascade activates signaling molecules that trigger key cellular actions of insulin. (See sidebar.) This complex process is the subject of intensive ongoing research.

Insulin signaling is disrupted in the states of insulin resistance and diabetes. The disruption of the insulin cascade provides a mechanism for the observed cluster of diabetes-associated diseases. Disruption of the insulin signaling cascade causes:

Disruption of the insulin cascade provides a mechanism for the observed cluster of diabetes-associated diseases.

- Failure of glucose uptake, (due to dysfunction of the glucose transporter), causing hyperglycemia (elevated blood sugar).
- Disinhibition of VLDL synthesis, causing elevated levels of VLDL and triglycerides in the blood.
- Disruption of endothelial nitric oxide production (in the inner lining of blood vessels), causing a loss of vascular agility and flexibility and leading to vascular disease in the heart, brain, and peripheral arteries.

Emerging evidence suggests that dysfunction of the insulin cascade has adverse effects on neurological health. Thus, insulin resistance and diabetes are increasingly seen as contributing to the risks of Alzheimer's disease and cognitive decline. (See chapter 7.)

Toll-Like Receptors, Fatty Acids and Inflammatory Disruption of Insulin Signaling

As mentioned above, Toll-like receptors (TLRs) are a family of pattern-recognition receptors that activate the innate immune system in response to particular pathogen-associated molecular patterns (PAMPs). This built-in recognition insures a rapid immune response to key materials associated with potentially dangerous pathogens.

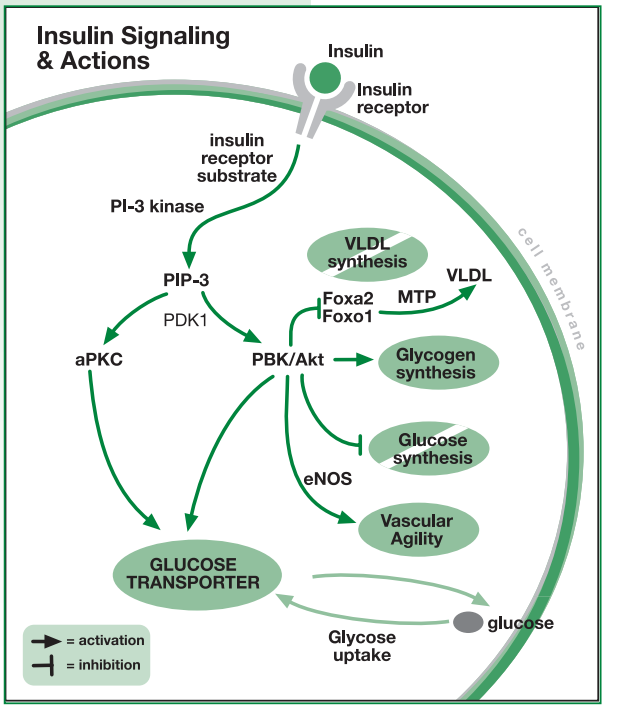
[k] *VLDL is the abbreviation for very low density lipoprotein.*

HOW *it* WORKS

The Insulin Cascade Links Metabolic and Vascular Signaling [91-95]

At the cellular level, insulin stimulates a cascade of signals (via enzymes known as kinases and phosphatases) that activate or inhibit transcription of various genes affecting metabolism, cell growth, and differentiation. For the purposes of this introduction, it is simplistically represented in this diagram as described below.

Insulin signaling is triggered by the arrival of insulin (the green circle in the diagram) at the insulin receptor. This initiates the activation (via tyrosine phosphorylation) of the insulin receptor itself, which then activates the insulin receptor substrate. A cascade of activations then occurs that stimulates other proteins that, in turn, activate the glucose transporter, causing glucose uptake into the cell. The cascade also stimulates glycogen synthesis (storing glucose), and prevents the synthesis of new glucose. The insulin cascade thus provides energy in the form of glucose for the cell to use. And it keeps glucose in the blood from rising to high levels that cause a variety of problems.



The insulin cascade also triggers the production of endothelial nitric oxide synthase (eNOS)—an enzyme that produces nitric oxide in the endothelium lining blood vessels. This allows blood vessels to dilate. When the insulin cascade is disrupted, the deficiency of eNOS results in rigid blood vessels prone to injury and disease (including hypertension and vascular disease in the heart, brain, and peripheral arteries).

The normally functioning insulin cascade also inhibits a set of signaling proteins that regulate fat synthesis—the Forkhead transcription factors[l] (Foxa2, Foxo1). When activated, these promote synthesis of saturated fat and triglycerides[m] and the secretion of the lipoprotein VLDL (which carries triglyceride) by the liver. The deregulation of the Foxa2-cascades—which occurs in the state of insulin resistance and diabetes—is emerging as a key mechanism in the development of dyslipidemia in diabetes and insulin resistance.[96]

A variety of inflammatory signaling molecules can interrupt insulin signaling at several sites along the cascade.[n] [97] One of the key implicated signaling proteins is JNK,[o] which is emerging as a central metabolic regulator in the development of insulin resistance in obesity. JNK is activated by fatty acids, cytokines (including TNFa) and other factors.[p] [98]

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[l] *Transcription factors orchestrate the expression of groups of genes, resulting in the synthesis of a group of proteins that may then have a number of effects.*

[m] *The actions of Foxa2 are mediated in part by the up-regulation of microsomal triglyceride transfer protein (MTP) and down-regulation of mitochondrial beta-oxidation of fatty acids.*

[n] *This is accomplished by removing activating tyrosine-phosphorylations or by creating inhibitory serine-phosphorylations. For example, the phosphatase PTP-1B (protein tyrosine phosphatase 1B) is implicated in the inactivation of the insulin receptor and the insulin receptor substrate. PTEN (phoshatase and tensin homolog deleted on chromosome ten) and SHIP2 (Src homology domain-containing inositol phosphatase) both remove activating phosphorylations from the key insulin signaling protein PIP3, resulting in the inhibition of insulin signaling.*

[o] *Other members of the mitogen-activated protein (MAP) kinase family—which includes JNK – are also implicated in the disruption of insulin signaling. These include ERK1/2 and p38.*

[p] *In genetic and dietary models of obesity, interruption of JNK1 activity prevents the development of insulin resistance and diabetes in mice.*

Lipopolysaccharide (LPS), associated with the cell wall of common bacteria, is the best recognized stimulant of TLR activation.[q] [99]

The activation of TLR4, the most studied of the Toll-like receptors, causes inflammation and a variety of downstream consequences. These consequences include the disruption of insulin signaling and its associated problems—hyperglycemia, elevated triglycerides/VLDL, reduced nitric oxide production, and increased risks for cardiovascular disease and Alzheimer's disease.

The activation of TLR4, the most studied of the Toll-like receptors, causes inflammation and a variety of downstream consequences.

Recent evidence demonstrates that nonmicrobial substances[r] can also activate TLRs or may heighten the TLR response to a pathogen.[100] [101] In particular, a substantial body of evidence (summarized by Lee and Hwang 2006)[102] indicates that TLR4 activation is also triggered or exacerbated by saturated fat. In addition, omega-3 fatty acids have been shown to reduce TLR4 stimulation by saturated fat and LPS.[103-106] Other poly- and monounsaturated fats also inhibit TLR activation, though they are far less effective than omega-3 fatty acids.[107]

Thus, the modulation of TLR4 by fatty acids provides a mechanism that may explain some of the emerging links between dietary fatty acids—notably saturated fats and omega-3s—and chronic inflammatory disease, including cardiovascular disease, hyperlipidemia, and possibly diabetes.[108-111] The interaction of fatty acids, LPS, TLR, and insulin cell signaling provides a sub-cellular framework that may explain, at least in part, the observed Western chronic disease cluster and its relation to the Western dietary pattern.

Limited data (neurobiological and nutritional epidemiology) suggest that TLR4 activation may play a role in Alzheimer's disease as well. Little evidence is available at this time to clarify whether TLR4 activation, with or without saturated fat or LPS exposure, may play a role in Parkinson's disease. However, LPS has been shown to cause dopaminergic degeneration in vitro and in vivo, suggesting the possibility of a TLR4 mechanism in Parkinson's disease that merits further investigation. (See chapter 8.)

A summary of some of the key studies linking TLR4 and/or its ligands (triggers) with chronic disease is provided in the diagram below.[112-132]

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[q] *TLRs were first recognized for their role in normal dorsal-ventral pattern development on Drosophila fruit fly embryos. Later it was discovered that TLRs initiate immune responses. To date, approximately 11 kinds of TLRs have been identified in humans. In general, the molecular patterns of PAMPs are highly conserved in evolution. The mechanism by which each TLR recognizes its particular PAMP is not yet well understood.*

[r] *These include select lipids, carbohydrates, nucleic acids and proteins including heat shock proteins, fibrinogen and minimally modified LDL.*

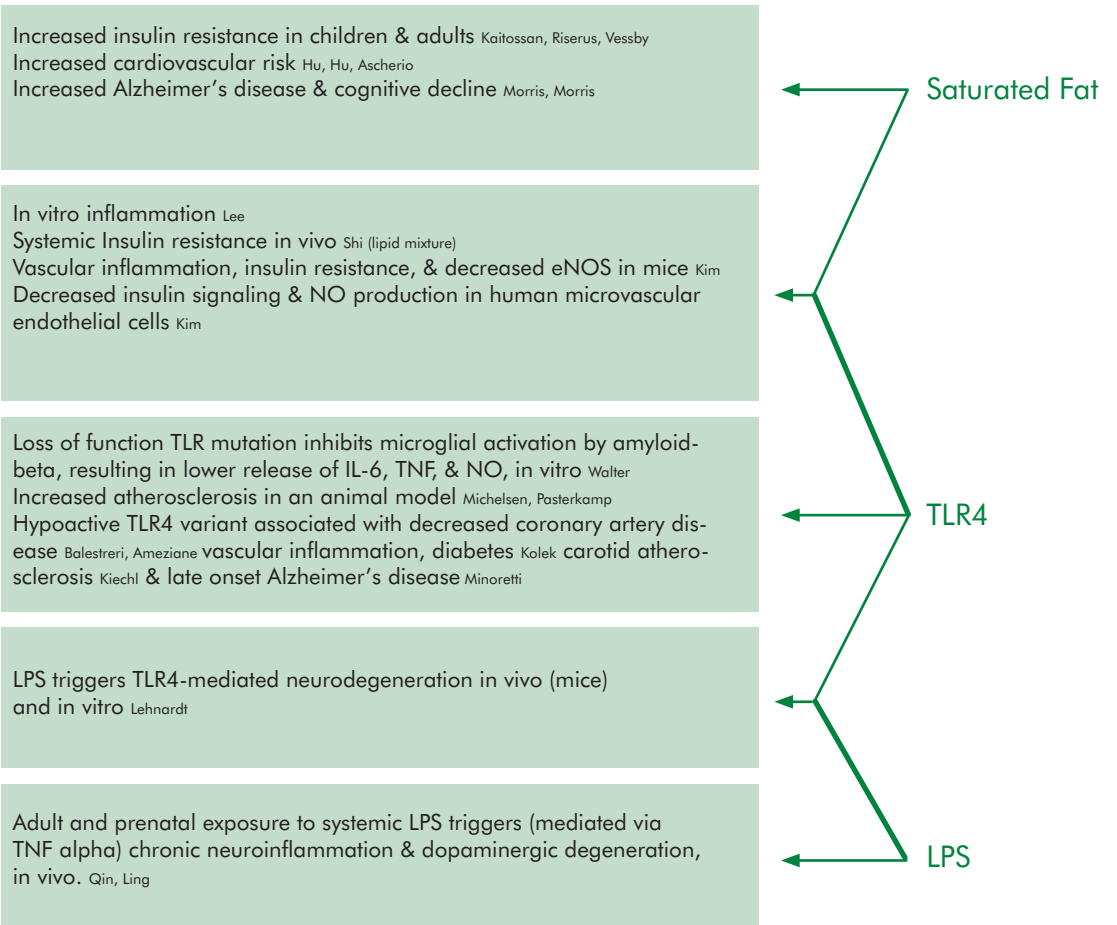
Are Novel Nutrients Driving Chronic Inflammation and Aberrant Metabolism?

Changes in the food supply over the past century—especially the growth of factory farming, processed, and "fast" food—have radically altered the American diet. As a result, that diet, for many people, is now characterized by high intakes of refined carbohydrates, saturated, and omega-6 fats; and low intakes of fiber, omega-3 fatty acids, fruits, and vegetables. Separately and as a group, these dietary characteristics are linked to many of the major health problems of Western society.

A variety of human and animal studies over the past 15 years suggest that this relatively new dietary pattern contributes to a cascade of inflammation, insulin resistance, dyslipidemia, and vascular

The modulation of TLR4 by fatty acids provides a mechanism that may explain some of the emerging links between dietary fatty acids...and chronic inflammatory disease.

TLR4, TLR4-Ligands & Chronic Disease
A Summary of Selected Evidence



This relatively new dietary pattern contributes to a cascade of inflammation, insulin resistance, dyslipidemia, and vascular dysfunction.

dysfunction. Two of the nutrients of particular concern, which act as inflammatory drivers in this pathway, are saturated fat and high-glycemic carbohydrates, (carbohydrates that are rapidly absorbed into the blood, causing sudden spikes in blood glucose and insulin).

A considerable body of evidence links high-glycemic diet with chronic disease.[s] Among the several hundred studies published since the concept of glycemic index was first proposed in 1981, most report health benefits with a diet of low-glycemic foods.[133]

Also emerging as key inflammatory features of the Western diet are the deficiencies of omega-3 fatty acids and essential micronutrients. The sidebar *Eicosanoids: Inflammatory Mediators Derived From Omega-6 and Omega-3 Fatty Acids* describes the predominantly inflammatory effects of omega-6–derived eicosanoids[t] and the generally balancing, anti-inflammatory effects of those derived from omega-3s.

Each of these components of the current inflammatory nutrient pattern also represents relatively recent developments in the human diet in the timeframe of human evolution.[134 135]

These features of the Western diet can be integrated into a novel-nutrient inflammatory-metabolic framework (based on the TLR and insulin signaling cascades). While this is a selective, simplified representation, it provides a glimpse of the web of connections among nutrition, cell signaling, inflammation, metabolism, and the Western disease complex. These interactions underscore the importance of particular dietary patterns as contributing *and preventable* causes of Western diseases. The power of nutrition to profoundly alter public health is further demonstrated by clinical nutrition studies (both observational and randomized controlled trials).

Of note, the fatty acids synthesized by the liver in these circumstances are largely saturated fatty acids.[139-142 u] Thus, the cascade begun by the action of saturated fat on the Toll-like receptor, or by the elevation of glucose and insulin due to high-glycemic carbohydrate, ultimately leads to the production of saturated fat, which may continue to feed the cycle of inflammation.

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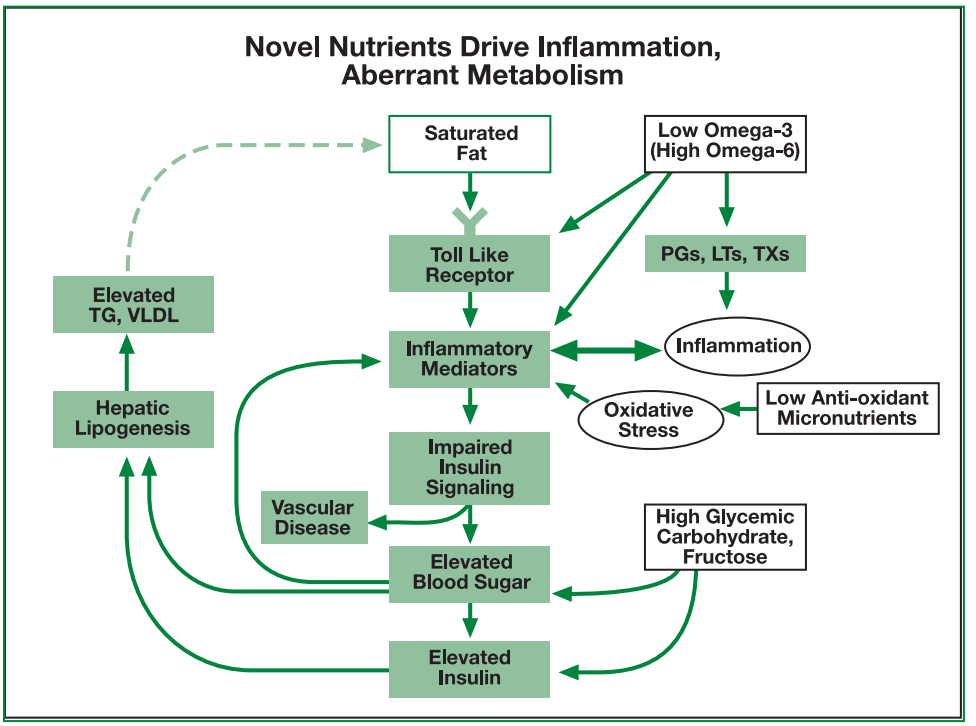
[s] *This evidence includes includes metabolic studies, short- and medium-term randomized trials, and long-term epidemiologic observations.*

[t] *Omega-6–derived inflammatory mediators include the pro-inflammatory 2-series prostaglandins and thromboxanes and the 4-series leukotrienes. The omega-3–derived 3-series prostaglandins and 5-series leukotrienes are less inflammatory or anti-inflammatory. See the sidebar "Eicosanoids: Inflammatory Mediators From Omega-6 and Omega-3 Fatty Acids" for further detail and references.*

[u] *Palmitic acid (a saturated fat) is the major fatty acid synthesized by the liver.*

The relative scarcity of omega-3 fatty acids in the Western diet also contributes to this inflammatory-metabolic pathway at multiple points. Omega-3 fatty acid deficiency allows Toll-like receptor stimulation by saturated fat to go unopposed. Further, low omega-3s in conjunction with elevated omega-6 fatty acids may promote a pro-inflammatory eicosanoid (PGs, LTs, TXs) profile.



While there are multiple entry points in this inflammatory-metabolic pathway, we begin, for the sake of discussion, with consumption of saturated fat. This produces inflammation through the Toll-like receptor, causing elevations of inflammatory mediators, such as NFkB, tumor necrosis factor (TNF) and other cytokines. (Note that LPS—originating from bacterial infection or lipid-mediated gut absorption, as previously described—can also stimulate inflammation through the Toll-like receptor.) That inflammation inhibits the insulin receptor and its downstream signaling, resulting in dysfunction of the glucose transporter. Without a functional glucose transporter to bring glucose into the cell, blood sugar rises, causing commensurate elevations of insulin. Elevations of blood glucose and insulin increase the synthesis and secretions of fat by the liver (a process called hepatic lipogenesis). This is driven in part by the greater quantity of glucose delivered to the liver, providing substrate for lipid synthesis. Elevated glucose and insulin also increase fat synthesis by stimulating transcription factors that up-regulate key lipogenic enzymes. These, in turn, increase the synthesis of triglyceride (TG), which is secreted into the bloodstream as VLDL. These consequences of insulin disruption promote the hypertriglyceridemia (elevated blood triglycerides) typically associated with diabetes.[v] [137] [138] Disrupted insulin signaling also blocks the production of nitric oxide within blood vessels. This leads to impaired vascular flexibility, promoting vascular injury and ultimately blood vessel disease (cardiovascular, peripheral vascular, and cerebrovascular disease) associated with diabetes.

[v] *Emerging evidence suggests that triglyceride elevations in the nonfasting state—which individuals are in most of the time—are an important risk factor for atherosclerosis (the main cause of heart attacks and strokes).*

High-glycemic carbohydrate, as indicated in the diagram, can also promote the inflammatory metabolic pathway by causing acute elevations of glucose and insulin, promoting further hepatic lipogenesis.

And finally, low levels of antioxidant micronutrients (including vitamins E, C, and polyphenols) allow higher levels of oxidative stress to occur. This promotes activation of transcription factor nuclear factor kappa B (NFkB) and further increases the expression of pro-inflammatory cytokines.

Anti-Inflammatory Omega-3 Fatty Acids—An Essential Nutrient Gone Missing

While there is still much to be learned about fatty acids, a growing body of evidence links omega-3s to protection against a variety of common illnesses. The benefits of omega-3s are well established for reducing cardiovascular disease and elevated triglycerides.[151] [152] In addition substantial evidence links omega-3s to the reduction of risks for depression,[153] ADHD and related developmental problems,[154-159] and Alzheimer's disease. (See chapter 7.) There is also suggestive but as yet inconsistent evidence of a role of omega-3 fatty acid deficiency in rheumatoid arthritis,[160] [161] asthma,[162] [163] and other illnesses increasingly linked to excessive inflammation.[164]

Changes in animal husbandry are also reducing omega-3s in the food supply.

Omega-3s have been largely removed from many sectors of the globalized food system, in part because they are susceptible to oxidation, or spoilage, due to their chemical structure. They are thus fundamentally incompatible with a food supply built around long shelf life and long-distance shipping. As omega-3 fats have diminished in the food supply, they have been replaced largely by omega-6 fats, which are less susceptible to spoilage. Changes in animal husbandry are also reducing omega-3s in the food supply. Since omega-3s enter the food chain from chloroplasts of green plants, the replacement of grazing farms—where animals freely consumed green vegetation—by grain-feeding on factory farms has diminished the omega-3 content of dairy, beef, chicken, and other animal products. Instead, these products contain increased levels of saturated fat, due to overfeeding and confinement, and omega-6s, which are contained in grain.[165-168]

The relative scarcity of omega-3 fatty acids contributes to the cascade of inflammation described above. Omega-6 fatty acids,

HOW *it* WORKS

Eicosanoids: Inflammatory Mediators Derived from Omega-6 and Omega-3 Fatty Acids

Eicosanoids are a family of inflammatory mediators—including the prostaglandins (PG), leukotrienes (LT) and thromboxanes (TX)—that are derived from omega-6 and omega-3 fatty acids that are 20 carbons in length. (The carbon chains that form the fatty acid backbone vary from a few up to 30 carbons in length.) Elevated inflammatory eicosanoid levels are commonly seen in blood or tissues from patients with acute and chronic inflammatory conditions. Metabolism of the omega-6 20-carbon fatty acid (arachidonic acid) by the cyclooxygenase enzyme (COX) produces the inflammatory 2-series PGs and TXs. Inflammatory cell production of COX-2, (an inducible form of the COX enzyme),[143] in turn, is triggered by immune stimulation, which increases the production of PGs.[144] PGE2, for example, causes fever, vascular permeability, and vasodilation, and increases pain and inflammatory swelling caused by other agents. PGE2 has also been shown to induce COX-2, thereby up-regulating its own production.[w] Metabolism of omega-6 arachidonic acid by the 5-lipoxygenase enzyme (LOX) produces the leukotriene (LT)4 series.[145] [146] LTB4 increases vascular permeability, leukocyte chemotaxis, and increased production of reactive oxygen species and inflammatory cytokines like TNF-a, IL-1 and IL-6. Other LTs of this series[x] are bronchoconstrictors and are implicated in the pathogenesis of asthma.[y] Thus, omega-6–derived eicosanoids have a spectrum of predominantly inflammatory effects.

Metabolism of the omega-3 20-carbon fatty acid (eicosapentaenoic acid, or EPA), produces the 3-series eicosanoids, which have reduced inflammatory (or relatively anti-inflammatory) properties. For example, the EPA-derived LTB5 is 10- to 100-fold less potent in attracting inflammatory cells than LTB4. The EPA-derived PGE3 is a less potent inducer than PGE2 of COX-2 gene expression in fibroblasts and of IL-6 production by macrophages. Recent studies have also identified a novel group of mediators formed from EPA and DHA by the action of COX-2/LOX enzymes, called E-series resolvins, which appear to exert anti-inflammatory and inflammation-resolving actions.[147]

Key fatty acids—from both the omega 3 and 6 families—are essential in the diet, meaning that we need them and cannot manufacture them from scratch. We can elongate fatty acids (producing the long-chain fatty acids from shorter chains that are more readily available in the diet), but we cannot convert fatty acids from one omega fatty acid family to another. Thus, consuming both omega-3s and -6s is important. Since omega-6s are generally abundant in the food supply, while omega-3s are scarce, achieving a less-inflammatory eicosanoid profile requires improving dietary omega-3 consumption.

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[w] *PGE2 also induces production of the inflammatory cytokine IL-6 by macrophages. Adding to the complexity, PGE2 can also cause anti-inflammatory effects, thus demonstrating, like many other eicosanoids, the capacity to cause both inflammatory and anti-inflammatory effects.*

[x] *Other 4-series leukotrienes include LTC4, D4 and E4.*

[y] *Leukotriene inhibitors (such as montlukast, zafirlukast, or zileuton) are commonly used for long-term asthma control.*

Glossary

Other Inflammatory Mediators

Cytokines - proteins secreted by immune and related cells (including fat and endothelial cells) that are involved in virtually every aspect of immunity and inflammation, including the initiation of the innate immune response. Cytokines affect cell growth, differentiation, and activation functions that affect the immune response.[148]

Chemokines - a family of cytokines that cause the migration of inflammatory and noninflammatory cells to various tissues. Chemokines have been implicated in inflammation, autoimmune diseases, and infection by HIV-1.[149]

Vascular adhesion proteins - molecules located on the surface of endothelial cells (the inner lining of blood vessels) that bind to inflammatory cells, allowing them to enter local tissues. Examples include - intracellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1) and E-selectin.

Transcription factors - key substances that regulate the expression of groups of genes. These genes then produce proteins that have roles in inflammation, metabolism, or other processes. Nuclear factor kappa B (NFkB) is an example of a transcription factor that plays an important role in the production of pro-inflammatory cytokines and other proteins. NFkB is activated in particular by oxidative stress.[150]

which are also essential for many biological functions, may have both inflammatory and anti-inflammatory effect through a variety of mechanisms.

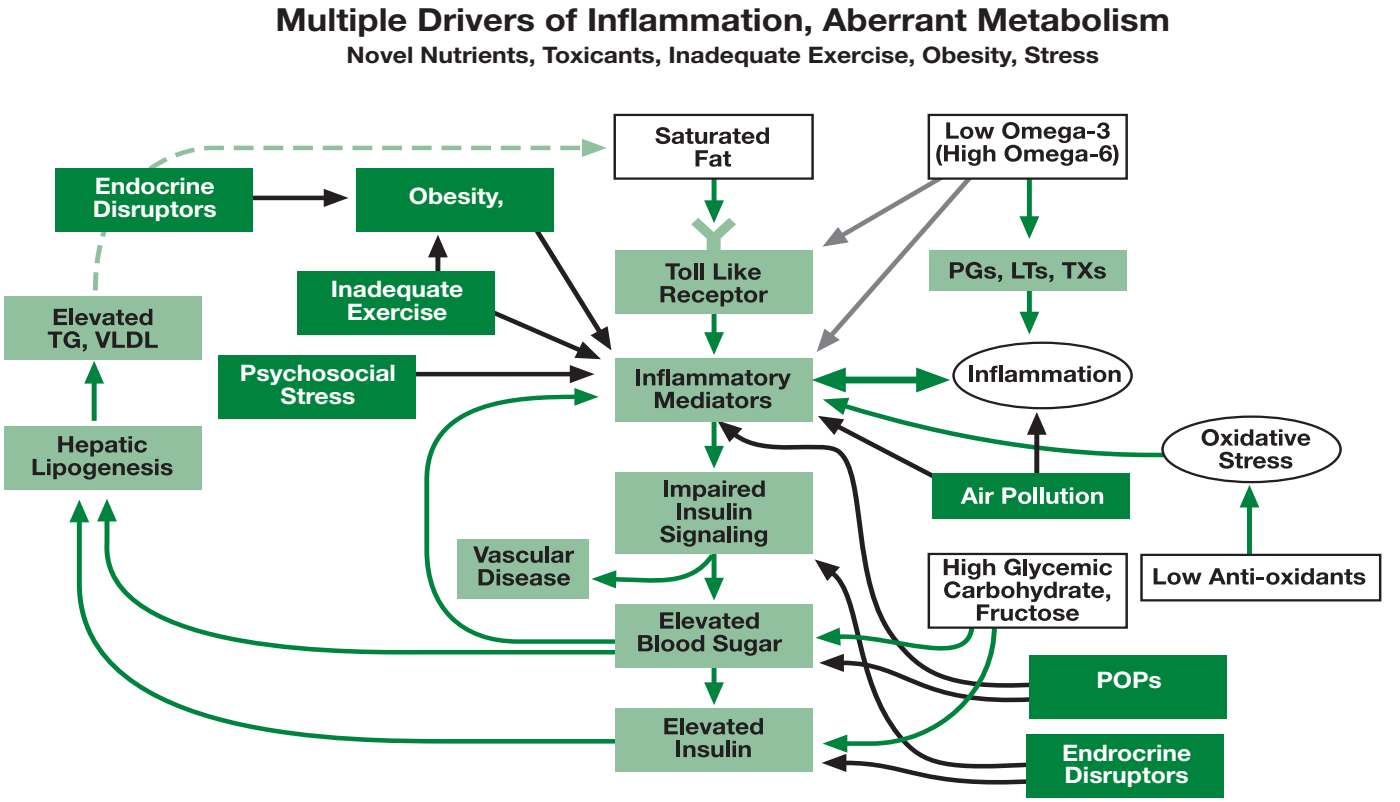
A variety of data suggests that omega-6s and -3s are in a healthy balance when their ratio is between 1:1 and 4:1,[169] though not all studies are consistent.[170] The average American diet has a ratio of about 17:1. The *Approaches To Healthy Living* in Chapter 9 provide dietary measures that increase omega-3 consumption, improve the balance of omega-3s and omega-6s, and enhance nutrition in general.

Inflammatory-Metabolic Pathway Compounded by Multiple Environmental Factors and Conditions: Inflammatory Chemicals, Lack of Exercise, Obesity, and More

While dietary factors are extremely important, the inflammatory-metabolic pathway is also likely to be driven by a variety of other factors that up-regulate inflammatory (and in many cases oxidative stress) pathways. These factors include various industrial chemicals and pesticides, inadequate exercise, obesity and psychosocial stress.

Examples of inflammatory chemical pollutants include air pollution (including ultrafine particles), endocrine disruptors such as bisphenol A and nonylphenol, and persistent organic pollutants such as some forms of dioxin and PCBs. Key points of impact of each of these factors on the inflammatory-metabolic pathway are shown in the diagram below. While only a few chemicals have been studied in this regard, such effects may not be unusual among the many hundreds of chemicals to which populations are routinely exposed. The cumulative impact of multiple inflammatory chemical exposures may therefore be considerable.

Bisphenol A is an example of a chemical contaminant with inflammatory-metabolic effects. According to biomonitoring studies, exposures to bisphenol A, a component of polycarbonate plastic and various resins and sealants, are common in the general population. Low-level exposure to bisphenol A in mice resulted in the development of elevated insulin levels and insulin resistance.[171] This hyperinsulinemic effect is a significant public health concern.[172] Bisphenol A and nonylphenol, (an endocrine disruptor used in plastic and petroleum processing and in surfactants), have also been shown to promote the development of fat cells in cell culture. (Specifically they accelerate the differentiation of adipocytes and increase the accumulation of fat in both adipocytes and hepatocytes.)[173] This suggests that bisphenol A and nonylphenol may independently



promote the development of obesity as well as hyperinsulinemia. A number of industrial chemicals, including pesticides, also inappropriately up-regulate oxidative stress, further stimulating the inflammatory cascade. (See chapter 8.)

In another example, exposure among the U.S. population to several persistent organic pollutants, or POPs, (in this case organochlorine chemical contaminants including some PCBs and dioxins, and several pesticides) has been shown to strongly correlate with the likelihood of having type II diabetes, insulin resistance, and metabolic syndrome.[174] [175]

Inadequate exercise is also associated with inflammatory-metabolic effects.[176] Exercise reduces the incidence of a variety of diseases associated with inflammation and oxidative stress, including cardiovascular disease, diabetes, and Alzheimer's disease. Paradoxically, exercise itself increases the production of ROS. This leads to up-regulation of antioxidant enzymes and enzymes that repair oxidative damage.[177] The net result is a decrease in oxidative damage

Exercise reduces the incidence of a variety of diseases associated with inflammation and oxidative stress, including cardiovascular disease, diabetes, and Alzheimer's disease.

and increased resistance to oxidative stress. Consistent with the link between oxidative stress and inflammatory cytokines, studies in people and animals show that exercise conditioning is associated with reduced inflammatory markers.[178]

Similarly, obesity is associated with increased inflammatory markers, possibly due to the increased secretion of inflammatory cytokines by adipose tissue.[179] This was illustrated in a study of identical twins with an average 18 kg intrapair difference in body weight, in which inflammatory markers were significantly higher in the obese members of the twin pairs.[180]

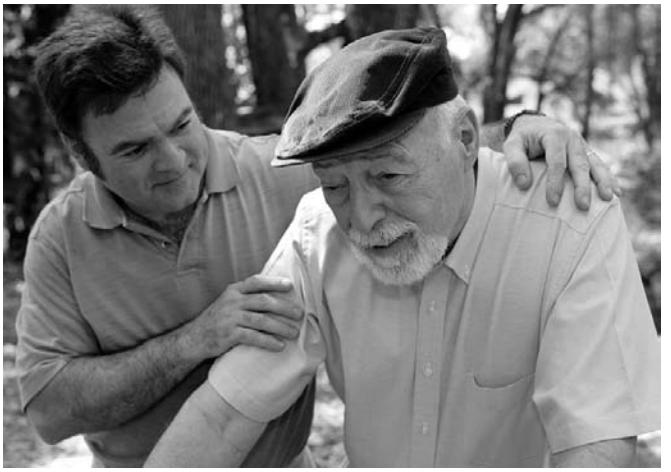
Air pollution[181-184] and psychosocial stress[185-187] are also associated with local or systemic inflammatory markers and may therefore contribute further to the drivers of inflammation and aberrant metabolism.

In the diagram above, multiple points of potential impact on the inflammatory-metabolic cycle have been simplified for the purposes of graphic presentation. The influence of these various factors on Alzheimer's/cognitive decline and Parkinson's disease will be discussed in chapters 7 and 8.

The Prevention Imperative Looms Large: Expanding the Environmental Paradigm to Include Diet and Exercise

Placing dementia/cognitive decline within the Western disease cluster has important implications for prevention. These diseases are highly responsive to preventive intervention. In fact, healthy diet and lifestyle have been associated with as much as an 83 percent lower risk for the development of cardiovascular disease[188] and a 91 percent lower risk for the development of diabetes type 2 among women[189] in long-term observational studies. Clinical intervention studies, (including several randomized studies[190-192]), have demonstrated reductions of approximately 50 percent in diabetes[193] and associated mortality[194] with diet and lifestyle intervention. Consumption of a Mediterranean-type diet by heart attack patients reduced recurrent heart attacks by 70 percent[195] and mortality by nearly 50 percent[196].

A variety of human observational and animal studies suggest that striking reductions may also be achieved in the incidence of dementia/cognitive decline with similar interventions. These data are reviewed in chapter 7.



Recognizing the significance of diet and exercise does not reduce the importance of toxicologic/chemical factors in neurodegenerative disease. In fact, diet, exercise, toxicants and social stress all influence the inflammatory-metabolic pathway. The few studies that have looked at multiple factors suggest they may interact in ways that are additive and possibly synergistic.[197 198]

Diet, exercise, toxicants and social stress all influence the inflammatory-metabolic pathway.

Conclusion

In this chapter we have considered cellular and subcellular mechanisms – especially inflammation and oxidative stress – that contribute to neurodegeneration and the associated illnesses in the Western disease cluster. We have introduced the insulin and Toll-like receptor (innate immune) signaling cascades as common mechanistic pathways in this disease cluster. We have seen how nutrition, toxicants, obesity, exercise, and stress may interact through an inflammatory-metabolic framework (based on these cascades) to increase risks for inflammation, diabetes and associated Western disease cluster illnesses. We turn now to the environmental influences themselves that act through these mechanisms to affect the risks of Alzheimer's disease, other dementias (chapter 7) and Parkinson's disease (chapter 8). As will be discussed, the considerable influence of these factors – alone and in combination – underscores the compelling opportunities at the personal, community and policy levels to reduce the risks for the Western disease cluster and neurodegenerative disease.

Endnotes

1. Lyon GR. Preface. Attention, Memory and Executive Function. Eds Lyon gr. Baltimore: Paul H. Brookes Publishing Co., 1996, p.xv.
2. Microbiology and immunology on line. University of South Carolina School of Medicine. http://pathmicro.med.sc.edu/ghaffar/complement.htm Accessed 10/16/07
3. O'Keefe JH et al. Dietary strategies for improving post-prandial glucose, lipids, inflammation, and cardiovascular health. Jl Amer College of Cardiology 2008;51:249-55.
4. Berg AH et al. Adipose tissue, inflammation, and cardiovascular disease. Circ Res. 2005;96:939-949.
5. Schmidt, MI et al. Diabesity: an inflammatory metabolic condition. Clin Chem Lab Med 2003;41(9):1120-1130.
6. Bruunsgaard H. The clinical impact of systemic low-level inflammation in elderly populations. Danish Medical Bulletin 2006;53(3): 285-309.
7. Calder PC. N-3 polyunsaturated fatty acids, inflammation, and inflammatory iseases. Am Jrnl of Clinical Nutrition 2006;83(6 suppl):1505S-1519S.
8. Watkins BA, Hannon K, Ferruzzi M, Li Y. Dietary PUFA and flavonoids as deterrents for environmental pollutants. J Nutr Biochem. 2007 Mar;18(3):196-205.
9. Wilson PW, Kannel WB, Silbershatz H, D'Agostino RB. Clustering of metabolic factors and coronary heart disease. Arch Intern Med. 1999 May 24;159(10):1104-9.
10. Eckel RH, Grundy SM, Zimmet PZ. The metabolic syndrome. Lancet. 2005 Apr 16-22;365(9468):1415-28.
11. Kalmijn S et al. Metabolic cardiovascular syndrome and risk of dementia in Japanese-American elderly men: the Honolulu-Asia aging study. Arterioscler Thromb Vasc Biol 2000;20:2255-2260.
12. Wilson PW, Kannel WB, Silbershatz H, D'Agostino RB. Clustering of metabolic factors and coronary heart disease. Arch Intern Med. 1999 May 24;159(10):1104-9.
13. Qiu C et al. The epidemiology of the dementias: an update. Curr Opin Psychiatry 2007;20:380-5.
14. Sonen JA et al. Pathological correlates of dementia in a longitudinal, population-based sample of aging. Ann Neurol 2007;62:406-413.
15. Jellinger KA et al. Prevalence and impact of cerebrovascular pathology in Alzheimer's disease and parkinsonism. Acta neurol Scand 2006;114:38-46.
16. Meigs, James B. The metabolic syndrome (insulin resistance syndrome or syndrome X) In UpToDate online medical text. UpToDate.com Accessed 8/13/08.
17. Ford ES et al. Prevalence of the metabolic syndrome among US adults. Findings from the third national health and nutrition examination survey. JAMA 2002;287:356-9.
18. Ross, Russell. Atherosclerosis: an inflammatory disease. NEJM. Jan. 14, 1999;340(2); 115-126.
19. Ridker Paul M et al. Comparison of C-reactive protein and low-density lipoprotein cholesterol levels in the prediction of first cardiovascular events. NEJM. Nov. 14, 2002;347(20):1557-1565.
20. Norris J et al. Omega-3 polyunsaturated fatty acid intake and islet autoimmunity in children at increased risk for type 1 diabetes. JAMA. Sept. 26, 2007;298,(12):1420-1428.
21. Atkinson MA, Maclaren NK. The pathogenesis of insulin-dependent diabetes mellitus. NEJM. 1994; 331:1428.
22. Shoelson SE, Lee J, Goldfine AB. Inflammation and insulin resistance. J Clin Invest. 2006 Jul;116(7):1793-801.
23. Kontgianni MD et al. Nutrition and inflammatory load. Ann NY Acad. Sci. 2006;1083:214-238.
24. Rutter M et al. C-reactive protein, the metabolic syndrome, and prediction of cardiovascular events in the Framingham Offspring Study. Circulation. 2004;110:380-5.
25. Rutledge A et al. Fructose and the metabolic syndrome: pathophysiology and molecular mechanisms. Nutrition Reviews. June 2007(II);65(6): S13-23.
26. Shi H, Kokeoeva MV, Inouye K et al. TLR4 links innate immunity and fatty acid-induced insulin resistance. Journal of Clinical Investigation.116(11):3015-3014.
27. Schmidt M et al. Diabesity: An inflammatory metabolic condition. Clin Chem Lab Med. 2003;41(19):1120-1130.
28. Launer LJ and Peila R. Inflammation and dementia: epidemiologic evidence. Acta Neurol Scand. 2006;114(Suppl 185):102-106.
29. Leo R, Di Lorenzo G, Tesauro M et al. Association between enhanced soluble CD40 ligand and proinflammatory and prothrombotic states in major depressive disorder: pilot observations on the effects of selective serotonin reuptake inhibitor therapy. J Clin Psychiatry. 2006 Nov;67(11):1760-6.
30. Kop wj, Gottdiner JS, Tangen CM et al. Inflammation and coagulation factors in persons > 65 years of age with symptoms of depression but without evidence of myocardial ischemia. Am J Cardiol. 2002 Feb 15;89(4):419-24.
31. Miller GE, Freedland KE, Duntley S, Carney RM. Relation of depressive symptoms to C-reactive protein and pathogen burden (cytomegalovirus, herpes simplex virus, Epstein-Barr virus) in patients with earlier acute coronary syndromes. Am J Cardiol. 2005 Feb 1;95(3):317-21.
32. Raisz LG et al. Pathogenesis of osteoporosis. In UpTo Date www.uptodate.com. accessed 6/2/08.
33. Lau FC, Shukitt-Hale B, Joseph JA. Nutritional intervention in brain aging: reducing the effects of inflammation and oxidative stress. Subcell Biochem. 2007;42:299-318.
34. Pratico D. Peripheral biomarkers of oxidative damage in Alzheimer's disease: the road ahead. Nuerobiology of Aging. 2005;26:581-583.
35. Cole GM, Lim GP, Yang F et al. Prevention of Alzheimer's disease: Omega-3 fatty acid and phenolic anti-oxidant interventions. Neurobiology of Aging. 2005;26S:S133-136.
36. Pratico D. Peripheral biomarkers of oxidative damage in Alzheimer's disease: the road ahead. Nuerobiology of Aging. 2005;26:581-583.
37. Lau FC, Shukitt-Hale B, Joseph JA. Nutritional intervention in brain aging: reducing the effects of inflammation and oxidative stress. Subcell Biochem. 2007;42:299-318. USDA-ARS, Human Nutrition Research Center on Aging at Tufts University, Boston, MA, USA.
38. Opara EC. Oxidative stress. Dis Mon. 2006;2:183-198.
39. Lau FC, Shukitt-Hale B, Joseph JA. Nutritional intervention in brain aging: reducing the effects of inflammation and oxidative stress. Subcell Biochem. 2007;42:299-318. USDA-ARS, Human Nutrition Research Center on Aging at Tufts University, Boston, MA, USA.
40. Ibid.
41. Opara EC. Oxidative Stress. Dis. Mon. 2006:2:183-198.
42. Ibid.
43. Migliore L et al. Searching for the role and the most suitable biomarkers of oxidative stress in Alzheimer's disease and in other neurodegenerative diseases. Neurobiology of Aging. 2005;26:587-595.
44. Smalheiser NR. Towards an animal mdel of Alzheimer's disease: can phorbol estes fan the flames? Alzheimer Research

Forum. www.alzforum.org/members/posters/Smalheiser/Smalheiser.html 2000.
45. Pratico D. Peripheral biomarkers of oxidative damage in Alzheimer's disease: the road ahead. Nuerobiology of Aging. 2005;26:581-583.
46. Lau FC, Shukitt-Hale B, Joseph JA. Nutritional intervention in brain aging: reducing the effects of inflammation and oxidative stress. Subcell Biochem. 2007;42:299-318. USDA-ARS, Human Nutrition Research Center on Aging at Tufts University, Boston, MA, USA.
47. Pratico D. Alzheimer's disease and oxygen radicals: new insights. Biochemical Pharmacology. 2002;63:563-567.
48. Lau FC, Shukitt-Hale B, Joseph JA. Nutritional intervention in brain aging: reducing the effects of inflammation and oxidative stress. Subcell Biochem. 2007;42:299-318. USDA-ARS, Human Nutrition Research Center on Aging at Tufts University, Boston, MA, USA.
49. Smith MA, Perry G. Free radical damage, iron, and Alzheimer's disease. J Neurol Sci. Dec 1995;134 Suppl:92-4.
50. Rottkamp CA, Raina AK, Zhu X, et al. Redox-active iron mediates amyloid-beta toxicity. Free Radic Biol Med. Feb 15, 2001;30(4):447-50.
51. Cole GM, Lim GP, Yang F et al. Prevention of Alzheimer's disease: Omega-3 fatty acid and phenolic anti-oxidant interventions. Neurobio of Aging. 2005;26S:S133-136.
52. Moriera P et al. The unbalance between metabolic and oxidative abnormalities and cellular compensatory responses in Alzheimer disease. Mechanisms of Ageing and Development. 2006;127:501-506.
53. Smith MA, Casadesus G, Joseph JA, Perry G. Amyloid-beta and tau serve antioxidant functions in the aging and Alzheimer brain. Free Radic Biol Med. 2002 Nov 1;33(9):1194-9.
54. Castellani RJ, Lee HG, Zhu X, Nunomura A, Perry G, Smith MA. Neuropathology of Alzheimer disease: pathognomonic but not pathogenic. Acta Neuropathol. 2006 Jun;111(6):503-9. Epub 2006 Apr 27.
55. Castellani RJ, Lee HG, Perry G, Smith MA. Antioxidant protection and neurodegenerative disease: the role of amyloid-beta and tau. Am J Alzheimers Dis Other Demen. 2006 Mar-Apr;21(2):126-30.
56. Pratico D. Alzheimer's disease and oxygen radicals: new insights. Biochemical Pharmacology. 2002;63:563-567.
57. Forman MS et al. Cortical biochemistry in MCI and Alzheimer disease: Lack of correlation with clinical diagnosis. Neurology. 2007;68;757-763.
58. Lau FC, Shukitt-Hale B, Joseph JA. Nutritional intervention in brain aging: reducing the effects of inflammation and oxidative stress. Subcell Biochem. 2007;42:299-318. USDA-ARS, Human Nutrition Research Center on Aging at Tufts University, Boston, MA, USA.
59. Ibid.
60. Ibid.
61. Okamoto T. NF-kB and rheumatic diseases. Endocr Meab Immune Disord Drug Targets. 2006 Dec;6(4):359-72.
62. Kimball J. Joseph W. Kimball's Biology Pages. http://users.rcn.com/jkimball.ma.ultranet/BiologyPages/I/Innate.html Accessed 10/15/07.
63. Cole GM, Lim GP, Yang F et al. Prevention of Alzheimer's disease: Omega-3 fatty acid and phenolic anti-oxidant interventions. Neurobio of Aging 2005;26S:S133-136.
64. Walter S et al. Role of the Toll-like receptor 4 in neuro-inflammation in Alzheimer's disease. Cell Physiol biochem 2007;20947-956.
65. Goldgaber D, Harris HW, Hla T et al. Interleukin 1 regulates synthesis of amyloid beta-protein precursor mRNA in human endothelial cells. Proc Natl Acad Sci U S A. 1989 Oct;86(19):7606-10.
66. Del Bo R, Angeretti N, Lucca E et al. Reciprocal control of inflammatory cytokines, IL-1 and IL-6, and beta-amyloid production in cultures. Neurosci Lett. 1995 Mar 16;188(1):70-4).
67. Misonou H. Morishima-Kawashima M. Ihara Y. Oxidative stress induces intracellular accumulation of amyloid beta-protein (Abeta) in human neuroblastoma cells. Biochemistry. 2000 Jun 13;39(23):6951-9.
68. Yan SD, Yan SF, Chen X et al. Non-enzymatically glycated tau in Alzheimer's disease induces neuronal oxidant stress resulting in cytokine gene expression and release of amyloid beta-peptide. Nature Medicine. 1995 Jul;1(7):693-9.
69. Moreira PI, Smith MA, Zhu X, Nunomura A, Castellani RJ, Perry G. Oxidative stress and neurodegeneration. Ann N Y Acad Sci. 2005 Jun;1043:545-52.
70. Nunomura A, Castellani RJ, Zhu X, Moreira PI, Perry G, Smith MA. Involvement of oxidative stress in Alzheimer disease. J Neuropathol Exp Neurol. 2006 Jul;65(7):631-41.
71. Kimball J. Kimball's Biology Pages. http://users.rcn.com/jkimball.ma.ultranet/BiologyPages/I/Innate.html Accessed 10/15/07.
72. Ibid.
73. Lee JY, Plakidas A, Lee WH et al. Differential modulation of Toll-like receptors by fatty acids: preferential inhibition by n-3 polyunsaturated fatty acids. Journal of Lipid Research 2003;44:479-486.
74. Ibid.
75. Munford R and Hall S. Detoxification of bacterial lipopolysaccharides (endotoxins) by a human neutrophil enzyme. Science. 1986;234:203–205.
76. Kitchens R, Ulevitch R, and Munford R. Lipopolysaccharide (LPS) partial structures inhibit responses to LPS in a human macrophage cell line without inhibiting LPS uptake by a CD14-mediated pathway. J. Exp. Med. 1992;176:485–494.
77. Lee JY, Hwang DH. The modulation of inflammatory gene expression by lipids: mediation through Toll-like receptors. Mol Cells. 2006 Apr 30;21(2):174-85.
78. Hwang D. Modulation of the expression of cylooxygenase-2 by fatty acids mediated through toll-like receptor 4-derived signaling pathways. FASEB J. 2001;15:2556-64.
79. Shi H, Kokeoeva MV, Inouye K et al. TLR4 links innate immunity and fatty acid-induced insulin resistance. Journal of Clinical Investigation. 116(11):3015-3014.
80. Lee JY, Hwang DH. The modulation of inflammatory gene expression by lipids: mediation through Toll-like receptors. Mol Cells. 2006 Apr 30;21(2):174-85.
81. Amar J, Burcelin R, Ruidavets J et al. Energy intake is associated with endotoxemia in apparently healthy men. Am J Clin Nutr 2008;87(5):1219-1223.
82. Cani P, Bibiloni R, Knauf C et al. Changes in gut microbiota control metabolic endotoxemia-induced inflammation in high-fat diet-induced obesity and diabetes in mice. Diabetes 2008;57(6):1470-1481.
83. Lee JY, Hwang DH. The modulation of inflammatory gene expression by lipids: mediation through Toll-like receptors. Mol Cells. 2006 Apr 30;21(2):174-85. Review.
84. Allport S. The Queen of Fats. University of California Press. Berkeley, CA. 2006.

85. Leheska JM, Thompson LD, Howe JC et al. Effects of conventional and grass feeding systems on the nutrient composition of beef. J Anim Sci. 2008 Jul 18. [Epub]
86. Cordain L, Eaton SB, Sebastian A et al. Origins and evolution of the Western diet: health implications for the 21st century. Am J Clin Nutr. 2005;81(2):341-54.
87. Bagga D, Wang L, Farias-Eisner R et al. Differential effects of prostaglandin derived from omega-6 and omega-3 polyunsaturated fatty acids on COX-2 expression and IL-6 secretion. Proc Natl Acad Sci U S A. 2003 Feb 18;100(4):1751-6. Epub 2003 Feb 10.
88. Das UN. A defect in the activity of delta-6 and delta-5 desaturases may be a factor in the initiation and progression of atherosclerosis. Prostaglandins, Leukotrienes and Essential Fatty Acids 2007;76: 251-68.
89. Lee JY, Hwang DH. The modulation of inflammatory gene expression by lipids: mediation through Toll-like receptors. Mol Cells. 2006 Apr 30;21(2):174-85. Review.
90. Mantzoros, Christos, Serdy, Shanti. Insulin action. In UpToDate online medical text. http://www.uptodate.com/online/content/topic.do?topicKey=diabetes/23821&selectedTitle=6~150&source=search_result Accesed 8/9/08.
91. Hirsch E et al. Phosphoinositide 3-kinases as a common platform for multi-hormone signaling. J of Endocrinology 2007;194:243-256.
92. Saltiel AR et al. Insulin signaling pathways in time and space. Trends in Cell Biology 2002;12(2):65-71.
93. Shi H, Kokoeva MV, Tzameli I, Yin H, Flier JS. TLR4 links innate immunity and fatty acid-induced insulin resistance. Journal of Clinical Investigation. 2006;116(11)3015-3025.
94. Rutledge A et al. Fructose and the metabolic syndrome: pathophysiology and molecular mechanisms. Nutrition Reviews. June 2007;65(6)(II):S13-23.
95. Wellen KE et al. Inflammation, stress and diabetes. J Clin Invest. 2005;115(5):111-119.
96. Rutledge A et al. Fructose and the metabolic syndrome: pathophysiology and molecular mechanisms. Nutrition Reviews. June 2007;(6) (II):S13-23.
97. Ibid.
98. Wellen KE et al. Inflammation, stress and diabetes. J Clin Invest. 2005;115(5): 111-119.
99. Lee JY, Hwang, Daniel H. The modulation of inflammatory gene expression by lipids: mediation through toll-like receptors. Mol Cells. 2006;21(2):174-85.
100. Ibid. Lee JY et al.
101. Kaisho T et al. Toll-like receptor function and signaling. J Allergy Clin Immunol 2007;117:979-87.
102. Lee JY, Hwang DH. The modulation of inflammatory gene expression by lipids: mediation through toll-like receptors. Mol Cells. 2006;21(2):174-85.
103. Lee JY et al. Differential modulation of toll-like receptors by fatty acids: preferential inhibition by n-3 polyunsaturated fatty acids. J Lipid Res. 2003;44:479-486.
104. Shi H, Kokoeva MV, Tzameli I, Yin H, Flier JS. TLR4 links innate immunity and fatty acid-induced insulin resistance. Journal of Clinical Investigation. 2006;116(11):3015-3025.
105. Lee JY et al. Saturated fatty acids, but not unsaturated fatty acids, induce the expression of cyclooxygenase-2 mediated through toll-like receptor 4. J of Biolog Chem. 2001;276(20):16683-16689.
106. Lee JY, Hwang DH. The modulation of inflammatory gene expression by lipids: mediation through toll-like receptors. Mol Cells. 2006;21(2):174-85.
107. Shi H, Kokoeva MV, Tzameli I, Yin H, Flier JS. TLR4 links innate immunity and fatty acid-induced insulin resistance. Journal of Clinical Investigation. 2006;116(11):3015-3025.
108. Lee JY, Hwang DH. The modulation of inflammatory gene expression by lipids: mediation through toll-like receptors. Mol Cells. 2006;21(2):174-85.
109. Norris JM, Yin X, Lamb MM et al. Omega-3 polyunsaturated fatty acid intake and islet autoimmunity in children at increased risk for type 1 diabetes. JAMA. 2007 Sep 26;298(12):1420-8.
110. Kaitosaari T, Rönnemaa T, Viikari J et al. Low-saturated fat dietary counseling starting in infancy improves insulin sensitivity in 9-year-old healthy children: the Special Turku Coronary Risk Factor Intervention Project for Children (STRIP) study. Diabetes Care. 2006 Apr;29(4):781-5.
111. Kaitosaari T, Rönnemaa T, Viikari J et al. Low-saturated fat dietary counseling starting in infancy improves insulin sensitivity in 9-year-old healthy children Diabetes Care 29(4):781-5,2006.
112. Risérus U. Fatty acids and insulin sensitivity. Curr Opin Clin Nutr Metab Care. 2008 Mar;11(2):100-5.
113. Vessby B et al. Substituting dietary saturated for monounsaturated fat impairs insulin sensitivity in healthy men and women: the KANWU study. Diabetologia. 2001;44:312-19.
114. Hu FB et al. Types of Dietary fat and risk of coronary heart disease: a critical review. J Am Col Nutr. 2001;20(1):5-19.
115. Hu FB et al. Dietary fat intake and the risk of coronary heart disease in women. N Eng Journ Med. 1997;337:1491-9.
116. Ascherio A et al. Dietary fat and risk of coronary heart disease in men: cohort follow up study in the United States. BMJ. 313(7049):84-90.
117. Morris MC et al. Dietary fats and the risk of incident Alzheimer Disease. Arch Neurol. 2003;60:194-200.
118. Morris MC et al. Dietary fat intake and 6-year cognitive change in an older biracial community population. Neurology. 2004;62:1573-1579.
119. Lee JY, Hwang DH. The modulation of inflammatory gene expression by lipids: mediation through toll-like receptors. Mol Cells. 2006;21(2):174-85.
120. Shi H, Kokoeva MV, Tzameli I, Yin H, Flier JS. TLR4 links innate immunity and fatty acid-induced insulin resistance. Journal of Clinical Investigation. 2006;116(11)3015-3025.
121. Kim F et al. Toll-like receptor-4 mediates vascular inflammation and insulin resistance in diet-induced obesity. Circ. Research. 2007;100:1589-1596.
122. Michelsen KS et al. Lack of Toll-like receptor 4 or myeloid differentiation factor 88 reduces atherosclerosis and alters plaque phenotype in mice deficient in apolipoprotein E. PNAS. 2004;101:10679-82.
123. Pasterkamp G et al. Role of Toll-like receptor 4 in the initiation and progression of atherosclerotic disease. European Journal of Clinical Investigation. 2004;34:328-334.
124. Walter S et al. Role of the toll-like receptor 4 in neuroinflammation in Alzheimer's Disease. Cell Physiol Biochem. 2007;20:947-956.
125. Ameziane N et al. Association of the toll-like receptor 4 gene asp299gly polymorphism with acute coronary events. Arterioscler Thromb Vasc Biol. 2003;23:e61-e64.
126. Balistreri CR et al. Role of Toll-like receptor 4 in acute myocardial infarction and longevity. JAMA. 2004;292:339-340.
127. Kolek MJ, Carlquist JF, Muhlestein JB, et al. Toll-like receptor 4 gene Asp299Gly polymorphism is associated with reductions in vascular inflammation, angiographic coronary artery disease, and clinical diabetes. Am Heart J. 2004;148(6):1034-40.

128. Kiechl S et al. Toll-like receptor 4 polymorphisms and atherogenesis. NEJM. 347(3):185-92.
129. Minoretti p et al. Effect of the functional toll-like receptor 4 Asp299Gly polymorphism on susceptibility to late-onset Alzheimer's disease. Neuroscience Letters. 2006;391:147-9.
130. Lenhardt S et al. Activation of innate immunity in the CNS triggers neurodegeneration through a toll-like receptor 4-dependent pathway. PNAS. 2003;100(14):8514-19.
131. Qin L et al. Systemic LPS causes chronic neuroinflammation and progressive neurodegeneration. Glia. 2007;55:45-462.
132. Ling, ZaoDung et al. In utero bacterial endotoxin exposure causes loss of tyrosine hydroxylase neurons in the postnatal rat midbrain. Movement Disorders. 2002;17(1):116-124.
133. Ludwig DS. Clinical update: the low-glycaemic-index diet. Lancet. 2007 Mar 17;369(9565):890-2. Review.
134. Cordain L, Eaton SB, Sebastian A et al. Origins and evolution of the Western diet: health implications for the 21st century. Am J Clin Nutr. 2005;81(2):341-54. Review.
135. Simopoulos AP. The importance of the ratio of omega-6/ omega-3 essential fatty acids. Biomed Pharmacother. 2002 Oct;56(8):365-79. Review.
136. (removed by author)
137. Nordestgaard, BG, Benn M, Schnohr P, Tybjaerg-Hansen A. Nonfasting triglycerides and risk of myocardial infarction, ischemic heart disease, and death in men and women. JAMA. 2007;298(3):299-308.
138. Bansal S, Buring JE, Rifai N, Mora S, Sacks FM, Ridker PM. Fasting compared with nonfasting triglycerides and risk of cardiovascular events in women. JAMA. 2007;298(3):309-316.
139. Gibbons G. Old fat, make way for new fat. Nature Medicine. 2005;11(7).
140. http://library.med.utah.edu/NetBiochem/FattyAcids/5_1.html Fatty Acid Synthesis and Modification Accessed 5/29/08.
141. Weickert MO, Pfeiffer AFH. Signaling mechanisms linking hepatic glucose and lipid metabolism. Diabetologia. 2006;49:1732-1741.
142. Rutledge A. Fructose and the metabolic Ssyndrome: pathophysiology and molecular mechanisms. Nutrition Reviews. June 2007;65(6)(II):S13-23.
143. Cook J. Eicosanoids. Crit Care Med. 2005;33(12 Sup):S488-S491.
144. Calder PC. Polyunsaturated fatty acids and inflammation. Prostaglandins, Leukotrienes and Essential Fatty Acids. 2006;75:197–202.
145. Penrose J. Physiology of lipid mediators (prostaglandins; leukotrienes; and lipoxins) and their role in inflammation. UpTo Date 2007. www.uptodate.com .
146. Peters-Golden M et al. Leukotrienes. NEJM. 2007;357: 1841-1854.
147. Calder PC. Polyunsaturated fatty acids and inflammation. Prostaglandins, Leukotrienes and Essential Fatty Acids. 2006;75:197–202.
148. Steinke JW et al. Cytokines and chemokines, J Allergy coin Immunol. 2006;117:S441-5.
149. Fernandez EJ et al. Structure, function, and inhibition of chemokines. Annu Rev Pharmacol Toxicol. 2002;42:469-99.
150. Linus Pauling Institute, Micronutrient Information Center. http://lpi.oregonstate.edu/infocenter/othernuts/la/index.html Accessed 8/9/08.
151. Lichtenstein AH, Appel LJ, Brands M et al. Summary of American Heart Association Diet and Lifestyle Recommendations revision 2006. Arterioscler Thromb Vasc Biol. 2006 Oct;26(10):2186-91. Review.
152. Wang C, Harris WS, Chung M, Lichtenstein AH, Balk EM, Kupelnick B, Jordan HS, Lau J. N-3 Fatty acids from fish or fish-oil supplements, but not alpha-linolenic acid, benefit cardiovascular disease outcomes in primary- and secondary-prevention studies: a systematic review. Am J Clin Nutr. 2006 Jul;84(1):5-17. Review.
153. Freeman MP, Hibbeln JR, Wisner KL, Davis JM, Mischoulon D, Peet M, Keck PE Jr, Marangell LB, Richardson AJ, Lake J, Stoll AL. Omega-3 fatty acids: evidence basis for treatment and future research in psychiatry. J Clin Psychiatry. 2006 Dec;67(12):1954-67. Review. Erratum in: J Clin Psychiatry. 2007 Feb;68(2):338.
154. Richardson AJ, Montgomery P. The Oxford-Durham study: a randomized, controlled trial of dietary supplementation with fatty acids in children with developmental coordination disorder. Pediatrics. 2005 May;115(5):1360-6.
155. Hibbeln JR, Davis JM, Steer C, Emmett P, Rogers I, Williams C, Golding J. Maternal seafood consumption in pregnancy and neurodevelopmental outcomes in childhood (ALSPAC study): an observational cohort study. Lancet. 2007 Feb 17;369(9561):578-85.
156. Sinn N, Bryan J. Effect of supplementation with polyunsaturated fatty acids and micronutrients on learning and behavior problems associated with child ADHD. J Dev Behav Pediatr. 2007 Apr;28(2):82-91.
157. Hirayama S, Hamazaki T, Terasawa K. Effect of docosahexaenoic acid-containing food administration on symptoms of attention-deficit/hyperactivity disorder - a placebo-controlled double-blind study. Eur J Clin Nutr. 2004 Mar;58(3):467-73.
158. Stevens L, Zhang W, Peck L, Kuczek T, Grevstad N, Mahon A, Zentall SS, Arnold LE, Burgess JR. EFA supplementation in children with inattention, hyperactivity, and other disruptive behaviors. Lipids. 2003 Oct;38(10):1007-21.
159. Richardson AJ, Puri BK. A randomized double-blind, placebo-controlled study of the effects of supplementation with highly unsaturated fatty acids on ADHD-related symptoms in children with specific learning difficulties. Prog Neuropsychopharmacol Biol Psychiatry. 2002 Feb;26(2):233-9.
160. Galarraga B, Ho M, Youssef HM et al. Cod liver oil (n-3 fatty acids) as an non-steroidal anti-inflammatory drug sparing agent in rheumatoid arthritis. Rheumatology (Oxford). 2008 May;47(5):665-9.
161. Goldberg RJ, Katz J. A meta-analysis of the analgesic effects of omega-3 polyunsaturated fatty acid supplementation for inflammatory joint pain. Pain. 2007 May;129(1-2):210-23. Epub 2007 Mar 1.
162. Mickleborough TD, Lindley MR, Ionescu AA, Fly AD. Protective effect of fish oil supplementation on exercise-induced bronchoconstriction in asthma. Chest. 2006 Jan;129(1):39-49.
163. Reisman J, Schachter HM, Dales RE, Tran K, Kourad K, Barnes D, Sampson M, Morrison A, Gaboury I, Blackman J. Treating asthma with omega-3 fatty acids: where is the evidence? A systematic review. BMC Complement Altern Med. 2006 Jul 19;6:26. Review.
164. Calder PC. n-3 polyunsaturated fatty acids, inflammation, and inflammatory diseases. Am J Clin Nutr. 2006 Jun;83(6 Suppl):1505S-1519S. Review.
165. Alport, Susan. The Queen of Fats: Why Omega-3s Were Removed from the Western Diet and What We Can Do to Replace Them. University of California Press. Berkeley, CA. 2006.

166. C.A. Daley, A. Abbott, M. Basurto et al.Omega-3/Omega-6 fatty acid content of Grass Fed Beef. College of Agriculture, California State University, University of California Cooperative Extension Service. http://www.csuchico.edu/agr/grsfdbef/health-benefits/ben-o3-o6.html . Accessed 8/18/08.
167. Cordain L, Eaton SB, Sebastian A et al. Origins and evolution of the Western diet: health implications for the 21st century. Am J Clin Nutr. 2005;81(2):341-54. Review.
168. Simopoulos AP. The importance of the ratio of omega-6/omega-3 essential fatty acids. Biomed Pharmacother. 2002 Oct;56(8):365-79. Review.
169. Simopoulos AP. The omega-6/omega-3 fatty acid ratio, genetic variation, and cardiovascular disease. Asia Pac J Clin Nutr. 2008;17 Suppl 1:131-4. Review.
170. Willett WC. The role of dietary n-6 fatty acids in the prevention of cardiovascular disease. J Cardiovasc Med (Hagerstown). 2007 Sep;8 Suppl 1:S42-5. Review.
171. Alonso-Magdalena P, Morimoto S, Ripoll C, Fuentes E, Nadal A. The estrogenic effect of bisphenol A disrupts pancreatic beta-cell function in vivo and induces insulin resistance. Environ Health Perspect. 2006;114(1):106-112.
172. Calafat A, Ye X, Wong L, Reidy J, Needham L. Exposure of the U.S. population to bisphenol A and 4-tertiary-octylphenol: 2003-2004. Environ Health Perspect. 2008;116(1):39-44.
173. Wada K et al. Life style-related diseases of the digestive system: endocrine disruptors stimulate lipid accumulation in target cells related to metabolic syndrome. Journal of Pharmacologial Sciences. 2007;105:133-137.
174. Lee D, Lee I, Jin S, Steffes M, Jacobs D. Association between serum concentrations of persistent organic pollutants and insulin resistance among nondiabetic adults: results from the National Health and Nutrition Examination Survey 1999-2002. Diabetes Care. 2007;30(3):622-628.
175. Lee D, Lee I, Porta M, Steffes M, Jacobs D. Relationship between serum concentrations of persistent organic pollutants and the prevalence of metabolic syndrome among non-diabetic adults: results from the National Health and Nutrition Examination Survey 1999-2002. Diabetologia. 2007;50(9):1841-1851.
176. Woods JA et al. Exercise, inflammation, and innate immunity. Neurol Clin. 2006;24:585-599.
177. Radak Z, Chung HY, Goto S. Systemic adaptation to oxidative challenge induced by regular exercise. Free Radic Biol Med. 2008 Jan 15;44(2):153-9. Epub 2007 Jan 23. Review.
178. Nicklas, BJ. Behavioural treatments for chronic systemic inflammation: effects of dietary weight loss and exercise training. CMAJ. 172(9):1199-209.
179. Ibid.
180. Rönnemaa T, Pulkki K, Kaprio J. Serum soluble tumor necrosis factor-alpha receptor 2 is elevated in obesity but is not related to insulin sensitivity: a study in identical twins discordant for obesity. J Clin Endocrinol Metab. 2000 Aug;85(8):2728-32.
181. Delfino RJ et al. Circulating biomarkers of inflammation, antioxidant acctivity, and platelet activation are associated with primary combustion aerosols in subjects with coronary artery disease. EHP, March 2008.
182. Goldberg MS et al. Associations between ambient air pollution and daily mortality among persons with diabetes and cardiovasccular disease. Environmental Research. 2006;100:255-267.
183. Brook, RD. Air Pollution, what is bad for the arteries might be bad for the veins. Arch Intern Med. 2008;168(9).
184. Elder Alison et al. Translocation and effects of unltrafine particles outside of the lung. Clinics in Oc and Env Medicine. 2006;5(4):785-96.
185. Kiecolt-Glaser JK, Belury MA, Porter K, Beversdorf DQ, Lemeshow S, Glaser R. Depressive symptoms, omega-6:omega-3 fatty acids, and inflammation in older adults. Psychosom Med. 2007 Apr;69(3):217-24. Epub 2007 Mar 30.
186. Johnson JD, O'Connor KA, Deak T, Stark M, Watkins LR, Maier SF. Prior stressor exposure sensitizes LPS-induced cytokine production. Brain Behav Immun. 2002 Aug;16(4):461-76.
187. Bierhaus A, Wolf J, Andrassy M et al. A mechanism converting psychosocial stress into mononuclear cell activation. Proc Natl Acad Sci U S A. 2003 Feb 18;100(4):1920-5. Epub 2003 Feb 10.
188. Stamper 00 – Primary prevention of coronary heart disease in women through diet and lifestyle. NEJM. 2000;343:16-22.
189. Hu FB et al. Diet, lifestyle, and the risk of type 2 diabetes mellitus in women. NEJM. 2001;4345:790-7.
190. Pan XR et al. Effects of diet and exercise in preventing NIDDM in people with impaired glucose tolerance: the Da Qing IGT and diabetes study. Diabetes. 1997;20(4):537-544.
191. Tuomilehto J et al. Prevention of the type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. NEJM. 2001;344(18):1343-50.
192. De Logeril et al. Mediterranean diet, traditional risk factors, and the rate of cardiovascular complications after myocardial infarction: final report of the Lyon diet heart study. Circulation. 1999;99:797-785.
193. Tuomilehto J et al. Prevention of the type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. NEJM. 2001;344(18):1343-50.
194. Eriksson KF, Lindgärde F. No excess 12-year mortality in men with impaired glucose tolerance who participated in the Malmö Preventive Trial with diet and exercise. Diabetologia. 1998 Sep;41(9):1010-6.
195. De Logeril et al. Mediterranean diet, traditional risk factors, and the rate of cardiovascular complications after myocardial infarction: final report of the Lyon diet heart study. Circulation 1999;99:797-785.
196. Barzi F et al. Mediterranean diet and all-causes mortality after myocardial infarction: results from the GISSI-Prevenzione trial. European Journal of Clinical Nutrition. 2003;57:604-11.
197. Hennig B, Ettinger AS, Jandacek RJ et al. Using nutrition for intervention and prevention against environmental chemical toxicity and associated diseases. Environ Health Perspect. 2007 Apr;115(4):493-5. Epub 2007 Jan 16
198. Watkins BA, Hannon K, Ferruzzi M, Li Y. Dietary PUFA and flavonoids as deterrents for environmental pollutants. J Nutr Biochem. 2007 Mar;18(3):196-205.

Chapter 7

Environmental Factors in the Development of Dementia

Focus on Alzheimer's Disease and Cognitive Decline

In this chapter we will review some of the evidence of the critical role of environmental factors in common forms of dementia, and in cognitive decline more generally. While a comprehensive review of the literature is beyond the scope of this report, we have tried to clarify some of the key drivers. We have limited this review to environmental chemicals, nutrition, health and social conditions, and exercise. We have not considered the potential role of infectious agents, cigarette smoking, caffeine, drugs of abuse, estrogen, and pharmaceuticals, among other factors.

In this chapter we treat several common forms of dementia as a continuum.

As discussed in chapter 5, a growing body of evidence suggests that various forms of neurodegeneration and associated symptoms may be viewed as a continuum. In this chapter we treat several common forms of dementia in particular as a continuum. Likewise, the lack of clear distinction between normal aging, abnormal cognitive decline, and dementia—in both symptoms and histopathology[1]—suggests that the degree of impairment can also be viewed as a spectrum.

In this chapter, we represent this spectrum of common dementias with the compound term "Alzheimer's disease/dementia." This allows us to discuss environmental factors that influence the larger spectrum of inter-related conditions and acknowledges frequently overlapping or mixed pathology. Similarly, we represent the spectrum of clinical severity with the terms "Alzheimer's disease/cognitive decline" or "dementia/cognitive decline." These broadly framed terms are consistent with the emerging view that cognitive decline—and the dementia it may lead to—are products of multiple interacting environmental and genetic influences. The wide variety of these influences is reflected in a continuum of pathologies and symptoms across diagnostic categories and degrees of severity.

The lobster is a symbol for long life and good fortune in Japan, and are especially associated with New Year's festivities and feasts.

We begin by addressing several preliminary subjects that provide a context for discussing environmental influences: the clinical picture of Alzheimer's/dementia, known genetic causes, and gene-environment interactions.

Alzheimer's Disease and Dementia—Clinical Features

Distinguishing normal aging from early dementia in practice is often very difficult.

In the clinical setting, Alzheimer's—like other forms of dementia—is defined as a decline in multiple cognitive functions, including memory, that is severe enough to interfere with daily functioning. The typical early symptoms, as defined by current convention, are difficult to distinguish from "normal" aging: gradual onset of short-term memory problems, language and visual-spatial perception difficulties, and declining executive function, including organizational abilities and efficiency. By definition, however, symptoms that tend to be sporadic, can be compensated for, and are generally non-progressive are considered normal aging. Symptoms that worsen over time and impair basic functions—such as speech fluency and the ability to prepare a meal or pay a bill—are by definition characteristic of dementia. Since the progressive nature of symptoms is key to the diagnosis, the determination that someone has dementia cannot be made at the onset of symptoms. Distinguishing normal aging from early dementia in practice is often very difficult.

The frequency of dementia is strongly related to age, with the prevalence nearly doubling every five years, from about 1.5 percent in 60–69-year-olds to 40 percent in 80–89-year-olds.[2] According to the conventional classification, Alzheimer's is the most common form of dementia, followed by vascular dementia, Lewy body dementia, and frontotemporal dementia.[3] (See chapter 5.)

Genetic Factors in Alzheimer's Disease

Inherited, Early-Onset Alzheimer's

Several genetic mutations increase amyloid-beta production or processing[a] and are associated with early-onset, familial forms of Alzheimer's disease—generally before age 60. Amyloid-beta is the primary constituent of extracellular plaques, typically considered one of the two pathological hallmarks of Alzheimer's disease, whether inherited or sporadic. The extent to which plaques and tangles (the other pathological hallmark), are responsible for neuron degeneration or merely markers of other fundamental processes gone awry continues to be debated, particularly with regard to the more common, late-onset form of the disease.

Amyloid-beta is generated by the cutting of a larger amyloid precursor protein by two enzymes, (beta and gamma secretase), a

[a] *by the gamma-secretase enzyme*

process that occurs in all cells in the body for reasons that are as yet unknown.[4] This process is increased in the aging brain, and much more so in the Alzheimer's brain. Once cut, fragments of amyloid-beta that lie outside the cell may aggregate into small, soluble molecules (oligomers) which can further concentrate into fiber-like structures. Oligomers are toxic to cultured neurons[5] [6] and interfere with learning and memory in studies with laboratory mice. [7]

Down syndrome, a genetic disorder caused by the presence of an extra chromosome (number 21) in the cells of affected individuals, also carries an increased risk for early-onset Alzheimer's disease and dementia.[8] Down syndrome is characterized by intellectual disabilities and various metabolic abnormalities. Postmortem examination of the brains of people with Down syndrome almost universally show amyloid plaques and tau tangles characteristic of Alzheimer's disease, beginning as early as age 8,[9] as well as evidence of excessive oxidative stress and lipid peroxidation.[10] [11] As in the general population, however, some people with Down syndrome with extensive amyloid-beta plaque formation survive into their seventies without evidence of dementia.

Several genes on chromosome 21 are likely to increase Alzheimer's disease risk. Their over-expression in people with Down syndrome, because of an extra copy of the chromosome, may help to shed light on the origins of Alzheimer's disease more generally. The amyloid precursor protein gene is located on chromosome 21 and its over-expression leads to excessive production of that protein. A nearby gene is responsible for producing a protein that influences cholesterol transport within the cell and appears to increase the likelihood that amyloid-beta plaques will form from the excessive levels of amyloid precursor protein.[12] A third nearby gene is responsible for producing the enzyme superoxide dismutase (SOD1). Over-expression of SOD1 contributes to an enzyme imbalance that results in excessive free-radical production, oxidative stress, and damage to critical cellular components.[13] One study concludes that excessive oxidative stress precedes the onset of plaque formation in people with Down syndrome.[14]

Individuals carrying the early-onset Alzheimer's genes have a high incidence of the disease and are affected at a relatively early age. However, these early-onset, genetically determined cases of the disease constitute a very small portion—between 4 and 6 percent—of all Alzheimer's cases.[15]

These early-onset, genetically determined cases constitute a very small portion – between 4 and 6 percent – of all Alzheimer's cases.

Genetics of Sporadic, Late-Onset Alzheimer's Disease—ApoE4

The more common, late-onset, sporadic form of Alzheimer's has no known genetic causes. However, the ApoE4 gene, according to most studies in the developed world,[16] [17] [18] increases the risks of developing Alzheimer's disease/dementia. At least one copy of the ApoE4 gene is typically reported to be present in about 15 percent of the US population[19] and in 5–41 percent of various populations around the world.[20] One meta-analysis found the risk of Alzheimer's disease in Caucasians to be increased approximately threefold in those carrying one copy (also called carriers, or heterozyotes) and nearly 15-fold in those carrying two copies (homozygotes) of the ApoE4 gene.[21] The risks among African Americans varied more between studies, averaging a 1.1 and 5.7-fold increase for African Americans carrying one and two copies of the gene, respectively. ApoE4 is also associated with a number of abnormalities in cognitive function in subjects without Alzheimer's disease.

One meta-analysis found the risk of Alzheimer's disease in Caucasians to be increased approximately threefold in those carrying one copy and nearly 15-fold in those carrying two copies of the ApoE4 gene.

Interestingly, the ApoE4 gene is also commonly (though not uniformly) associated with a variety of other diseases and conditions including vascular dementia, mild cognitive impairment,[22] [23] elevated LDL cholesterol,[24] and cardiovascular disease.[25] [26] [27] One meta-analysis found the cardiovascular risk in ApoE4 carriers increased 1.42-fold.[b] [28]

The ApoE gene plays a key role in lipid transport and processing. The ApoE lipoprotein that the gene produces carries lipid in the blood as well as in the brain, where it also transports and clears amyloid-beta.[c] [29] [30]

Beyond the Gene-Environment Dichotomy: Gene-Environment Interactions

Health and disease in the brain, as in any organ system, are influenced by multiple factors. By tradition, these factors are typically divided into genetic and environmental influences. In some cases, where a genetic or environmental influence is truly determinative, this dichotomy holds up.[d] More often, however, genetic and environmental influences interact.[e]

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[b] *The increased risk was relative to the more common ApoE3 genotype.*

[c] *ApoE in the brain is produced by astroglia and microglia, and ApoE receptors are expressed by neurons.*

[d] *An example is infantile Tay Sachs Disease, which is caused by a genetic error in fatty acid metabolism and is invariably fatal within the first few years of life.*

[e] *This is illustrated by the PKU (phenylketonuria) gene, which causes mental retardation in the context of a conventional diet. Importantly, by removing the amino acid phenylalanine from the diet beginning in infancy, (i.e. altering the environment), mental retardation is prevented.*

The ApoE4 gene provides an example of complex gene-environment and gene-gene-environment interactions. As mentioned above, ApoE4 increases risks for Alzheimer's and cardiovascular (among other) diseases, and Western lifestyle factors are emerging as key to these risks. This is illustrated in a 21-year Swedish observational study. It found that ApoE4 alone increased the risk for dementia/Alzheimer's disease by a factor of 2.83. When interactions with lifestyle factors were considered, the ApoE4-environment interactions increased the risk by a factor of 11.42. Environmental factors increasing risk included physical inactivity, alcohol drinking, smoking, and Western-type diet (specifically reduced intake of poly-unsaturated fat and increased intake of saturated fat). The authors concluded that lifestyle interventions may greatly modify dementia risk, particularly among genetically susceptible individuals.[31]

ApoE4 increases risks for Alzheimer's and cardiovascular diseases, and Western lifestyle factors are emerging as key to these risks.

A small body of cross-cultural epidemiologic studies also supports the view that Western lifestyle, including diet, is a key driver of ApoE4-associated risks. Several studies of Alzheimer's/dementia in Nigerian-Yoruba elders—who consume a low-fat, low-calorie, and predominantly plant-based diet[32] —found no significant association between ApoE4 and Alzheimer's/dementia. They also showed much lower age-adjusted rates of dementia/Alzheimer's disease. These findings contrasted sharply with the African-American control population in this study, which showed higher age-adjusted incidence of Alzheimer's and a significant association of ApoE4 with the disease.[33] [34] [35] [36] [37] [f]

Adding complexity, the ApoE-saturated fat interaction, mentioned above, can be further modified by additional genetic influences (for example, variations in an ApoE promoter gene).[38] Such gene-gene-diet interactions may explain inconsistent findings among previous studies examining ApoE4 as a risk factor for a variety of conditions. This also illustrates a more general point that the risk of many diseases is influenced by multiple genes and multiple environmental factors. These multiple factors constitute a virtual sea of conditions in which the influence of single factors may vary considerably.

Several large longitudinal studies have found that ApoE4 increases the risk of cognitive decline associated with atherosclerosis, peripheral vascular disease, and diabetes.[39] [40] Interestingly, one study examining the role of ApoE4 in chronic occupational lead exposure found that ApoE4 increased the adverse effect of lead on neurobehavioral function, including memory.[41] Each of these factors will be discussed below.

[f] *While the two populations had similar ApoE gene frequencies, the influence of other genetic factors cannot be ruled out as contributing to the different Alzheimer's/dementia rates in these two populations.*

Thus the effects of ApoE4 on the risks of Alzheimer's disease/cognitive decline increasingly appear to be influenced by environmental factors. The data suggest that modifying environmental factors may prevent the risks associated with ApoE4 and potentially a major portion of the Alzheimer's/dementia burden. Additional studies, discussed below, provide abundant evidence of environmental influences independent of ApoE4-related mechanisms as well.

We now turn more specifically to environmental contributions to Alzheimer's/dementia and cognitive decline.

... Modifying environmental factors may prevent the risks associated with ApoE4 and potentially a major portion of the Alzheimer's/ dementia burden.

Environmental Chemicals

Relatively few studies have examined the influence of toxic chemical exposures on the risk of dementia/cognitive decline. Nonetheless, evidence has begun to develop. Studies implicating lead, pesticides, PCBs, particulate air pollution, and aluminum have recently been published. In one recent study, 21 percent of more than a thousand patients presenting to a university clinic for cognitive disorders had histories suggestive of toxic environmental and occupational exposures. A history of toxic exposure significantly lowered the age of onset of cognitive decline, an effect equivalent in magnitude to that caused by carrying two copies of the ApoE4 gene.[42]

Lead

Lead is toxic to multiple organ systems, including the brain. Low-level lead exposures can impair cognitive function in children. Evidence indicates there is no exposure threshold below which harmful effects do not occur. Extensive evidence also shows that past adult lead exposure in the work setting increases the likelihood of cognitive impairment.[43] [44] More recently low-level cumulative exposure to lead outside of the work setting has been shown to adversely affect cognitive function including visual-spatial/visual-motor function, language, processing speed, executive function, verbal memory and learning, and visual memory.[45] One longitudinal study divided a population of elderly men into four groups (quartiles), based on the amount of lead found in patella bone. It found each quartile increase in bone lead was associated with approximately five years of additional cognitive aging as measured by the Mini-Mental Status Exam. This suggests that lead has a substantial impact on cognitive aging across the population. [46]

A variety of mechanisms may contribute to lead neurotoxicity. In its various forms, lead can cross the blood-brain barrier, disrupt

calcium-dependent enzymes and neurotransmitter metabolism[47] and release, and cause neuronal oxidative stress[48] and aggregation of amyloid-beta .[49] In addition, lead impairs synaptic transmission and plasticity,[50] oxidative phosphorylation, glucose oxidation, and microtubule synthesis,[51] among other effects. Lead has also been shown to preferentially affect the prefrontal cerebral cortex, hippocampus, and cerebellum.[52]

Another mechanism has recently been proposed whereby early-life lead exposure may contribute to late-life neurodegeneration. The mechanism—referred to as Latent Early-Life Associated Regulation, or LEARn—is suggested by a series of studies by Basha, Zawia, and others in rodents and monkeys. LEARn is an example of a more general phenomenon whereby early life conditions predispose to adult disease. In this instance, exposing fetal rodents to lead caused brief increases during neonatal life in key Alzheimer's disease–related proteins. This was followed by delayed over-expression of these proteins and amyloid-beta in late life—long after early lead exposure had ceased. Interestingly, exposure to lead during old age did not cause increases in the Alzheimer's disease–related proteins.

These data suggest that early developmental lead exposure may lead to increased expression of amyloid precursor protein later in life, increasing amyloid-beta production.

Recently the same delayed, late-life increase in Alzheimer's disease–related proteins was reported in aged monkeys exposed in infancy to low levels of environmental lead. In addition, these monkeys showed Alzheimer's (amyloid) plaques in the frontal association cortex, an Alzheimer's disease–related brain region, as well as biochemical evidence of epigenetic imprinting.[g] [53] Taken together, these data suggest that early developmental lead exposure may lead to increased expression of amyloid precursor protein later in life, increasing amyloid-beta production.[54] [55] While lead's role as a developmental toxicant has been evident for nearly a century, the neurodegenerative toxicity of lead in the brain[h] has only come into focus in the past decade or so. Thus, lead may now be considered a lifecycle neurotoxicant.

Aluminum

Dietary exposure to aluminum salts is nearly universal in the developed world as they are commonly added to commercially prepared foods and beverages. They are sometimes used to clarify drinking water, make salt free-pouring, color snack and dessert foods, and make baked goods rise.[56]

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[g] *The evidence of epigenetic imprinting included decreased DNA methyltransferase activity and higher levels of oxidative damage to DNA.*

[h] *It has long been known that lead causes impairment of peripheral nerves, which are outside of the brain.*

Dietary exposure to aluminum salts is nearly universal in the developed world as they are commonly added to commercially prepared foods and beverages.

The possible role of aluminum in Alzheimer's disease/dementia has been debated since 1965 when controversial evidence emerged showing that aluminum injections into the brain caused neurofibrillary tangle–like pathology. (The relevance of this data to human disease is questionable, given the high dose and route of exposure.)

Several studies conducted in recent years have resurrected old questions about the potential for aluminum to contribute to neurodegenerative disease. One recent small pilot study in rats showed that chronic exposure to dietary aluminum at doses within the range of the human exposure spectrum was associated with aluminum accumulation in hippocampal neurons.[57] A larger follow-up study in rats showed a dose-response relationship between dietary aluminum and memory loss. [58] The exposure level at which memory loss began to increase (0.49 mg aluminum/kg/day) was well within the range of human dietary exposure. Though estimates vary, one exposure study found that half of Americans ingest 0.34 mg aluminum/kg/day or less, 45 percent ingest 0.34–1.36 mg/kg/day, and 5 percent take in more than 1.36 mg/kg/day as additives in commercially processed foods and beverages.[59] A recent analysis of aluminum content of foods found that some varieties of baking powder, pancake/waffle mixes and frozen products, and ready-to-eat pancakes contained the most aluminum of foods tested. The aluminum contained in a single serving of some pancakes [60] [61] (up to 180 mg of aluminum, or 3 mg/kg for a 60 kg person), was the equivalent of five times the dose associated (when ingested chronically) with older-age memory loss in the rat study.[i] [62] This suggests that consuming the high-aluminum varieties of these foods on a daily basis could lead to exposures well above the level at which age-associated memory loss was observed in the rat study.

In another study, brain specimens from rats chronically exposed to high-end human levels of aluminum exposure showed microscopic changes commonly regarded as components of plaque and tangle formation.[j] [63] [64]

A recent laboratory study found that exposure of human neural cells to nanomolar concentrations of aluminum induced gene expression promoting inflammation and cell death, similar to that observed

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[i] *Since the determinants of aluminum absorption are not yet fully understood, it is difficult to predict the aluminum exposure from aluminum content of a meal.*

[j] *The brain histopathology of exposed rats included oxidative damage, inhibition of PP2A (protein phosphatase 2A) activity, hyperphosphorylated tau, and granulovacuolar degeneration. PP2A is a major phosphate-removing enzyme in the brain which is active against tau and neurofilament hyper-phosphorylation. Plaques and tangles per se do not develop in rats.*

in Alzheimer's disease.[k] [l] [65] While this supports a possible role for aluminum in Alzheimer's disease/dementia, the relevance of this laboratory observation to real world conditions is not yet established.

Thus, recent evidence reopens a debate and rekindles concerns that current dietary exposures to aluminum may increase the risk of dementia/Alzheimer's disease. It should be noted that aluminum absorption is complex and influenced by many factors—including pH, the molecular state of aluminum, other nutrients in the food, and possibly unidentified host factors.[66] [67] [68] Because the quantity of aluminum ingested is not by itself a predictor of aluminum absorption, identifying safe dietary limits is difficult. Nonetheless, the new animal data and current dietary levels of aluminum exposure create an urgent need for additional research and dietary guidelines. Both the European Food Safety Authority and the Joint Food and Agriculture/WHO Expert Committee on Food Additives recently lowered their recommended safe upper limit (provisional tolerable weekly intake) for aluminum from 7 mg/kg/week to 1 mg/kg/week.[69] [70] This new limit is 7 times more protective than the current US recommended limit (minimal risk level) of 1 mg/kg/day.[71]

...Recent evidence reopens a debate and rekindles concerns that current dietary exposures to aluminum may increase the risk of dementia/ Alzheimer's disease.

Iron, Copper, Zinc

Iron, copper, and zinc are biologically essential and are normally present in the brain, although their levels are fairly tightly regulated through mechanisms that are not well understood.[72] [73] In addition, iron accumulates in the same areas of the brain in which the amyloid-beta peptide accumulates.[74] When controls fail, these metals can increase oxidative stress by catalyzing the production of free radicals directly[75] or by binding amyloid-beta and thus catalyzing the production of free radicals.[76] While the links among metals, oxidative stress, and amyloid-beta provide plausible general mechanisms whereby these metals may cause neurodegenerative disease, few details are known. In addition, few epidemiologic studies have examined the possible contribution of biologically essential metals to Alzheimer's disease/dementia. (See chapter 8 for discussion of Parkinson's disease risk.)

Air Pollution

While air pollution is often thought of as harmful mainly to the lungs, a large body of evidence indicates that the cardiovascular system is also vulnerable to the effects of air pollution.[77] Emerging evidence suggests that air pollution contributes to brain inflammation

[k] *This study used DNA microarray data.*

[l] *Increased expression was observed for: NF-kB subunits, IL-1B precursor, cytosolic phospholipase A2, cyclooxygenase 2, and amyloid precursor protein).*

A growing body of evidence has begun to link air pollution with neurodegenerative disease.

and the risk of Alzheimer's-type neurodegenerative disease as well.

Air pollution is a complex mixture of gases (notably ozone, carbon monoxide, and nitrogen and sulfur oxides), metals (e.g., lead, manganese), volatile organic compounds from industrial and vehicular sources, particulates, and lipopolysaccharide (LPS), among other constituents. While many of these components have been linked with illnesses, recent evidence incriminates particulate matter in a variety of diseases in several organ systems.[78] Particulates are a complex mix of solids and liquids (including organic and elemental carbon, nitrates, sulfates, and metals) in various sizes ranging from a few nanometers (billionths of a meter) to 10 microns (millionths of a meter) in diameter. The major human source of air pollution in the modern world is the burning of fossil fuels in motor vehicles and by industry.[79]

Studies demonstrate a variety of cardiovascular effects from both short- and long-term exposures to particulates—even at present day levels—including reduced oxygen supply to the heart (myocardial ischemia) and heart attacks, heart failure, stroke, arrhythmia and sudden death, cardiovascular hospitalization and mortality, and venous thrombosis (blood clots).[80 81]

While the risk to any one person from air pollution at a given point in time is small, the pervasive, constant nature of the exposure results in profound health impacts on the population as a whole. Though the full extent of the consequences of air pollution are still uncertain, known adverse impacts on health already place the particulate component alone as the thirteenth leading cause of global mortality, causing approximately 800,000 deaths per year.[82]

A growing body of evidence has begun to link air pollution with neurodegenerative disease. This evidence includes human and animal studies that combine histopathology, neuroimaging, cognitive testing, and limited epidemiology. Much of this evidence is drawn from recent postmortem studies comparing brain tissue from lifelong residents of cities with severe air pollution with brain tissue from lifelong residents of low-air-pollution cities. (All of the individuals in the studies had been free of neurologic disease or symptoms before death, and had died sudden, non-neurologic deaths.) These studies showed evidence of inflammation and Alzheimer's type brain tissue pathology in the residents of polluted-air cities, compared to the residents of relatively clean-air cities. The pathology included numerous

inflammatory markers,[m] accumulation of amyloid-beta[n] (one of the key protein markers of Alzheimer's disease), inflammatory activation of endothelium (the cells lining the inside of blood vessels), oxidative stress, and inflammatory cells.[83] [84]

Particulate matter has been seen in red blood cells (erythrocytes) in blood vessels within the brain[o] [85] (and other organs), and in inflammatory cells within brain tissue surrounding the blood vessels.[86] The studies also showed disruption of the blood-brain barrier in residents of polluted-air cities, potentially allowing inflammatory mediators and ultrafine air pollution particles access to the brain from the bloodstream.[p] In addition, ultrafine pollution particles were identified in olfactory bulb neurons, a potential conduit for selected toxicants to travel from the nose to the brain[q] without the interference of the blood-brain barrier.[87] Whether particulate matter or other toxicants can actually move from the olfactory bulb to other areas of the brain in humans is not yet known. [88] [89] [90] This question is of particular interest because some olfactory pathways lead to areas of the brain that are key to learning and memory (including the entorhinal cortex and the amygdala).[91]

Exposure to air pollution is associated with neuroinflammation, an altered innate immune response in the brain, and accumulation of amyloid-beta.

Ultrafine particles that penetrate deeply into the lungs initiate an inflammatory response and may be absorbed directly into the circulating blood.[r] [92] Similarly, particle deposition in the nose causes inflammation and disruption of the olfactory barrier—potentially facilitating the transport of toxicants into the olfactory bulb.

Amyloid-beta was seen in 100 percent of young carriers of the ApoE4 gene (genotype ApoE4/3) from highly polluted areas, compared with 58.8 percent of ApoE3/3 subjects.[s] [93] This suggests that people carrying ApoE4 may be more susceptible to inflammatory neurodegeneration associated with air pollution. Alpha-synuclein, a

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[m] *Inflammatory markers included increased COX2 expression, IL-1B, and CD14.*

[n] *Amyloid-beta accumulation was documented in the frontal cortex, hippocampus and/or olfactory bulb.*

[o] *Inflammatory mediators—such as TNF-alpha or IL-1B—in the blood or endothelium can be transmitted across the blood-brain barrier into the brain.*

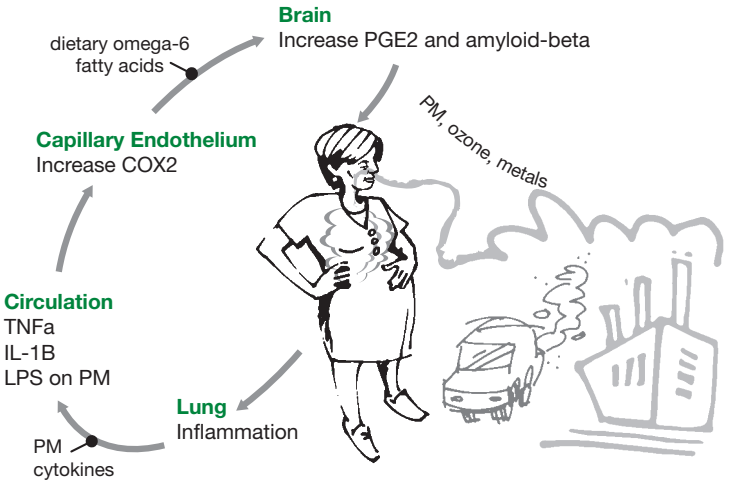
[p] *Ultrafine particulates are <100 nm in diameter. Only these very tiny particulates are small enough to pass from the lung into the bloodstream, and from there to potentially cross the blood-brain barrier.*

[q] *The olfactory pathway provides access in particular to areas of the brain that are critical for learning and memory.*

[r] *Particulate air pollution is highly inflammatory at the level of the lung and brain due to several inflammatory components. These components include bacterial lipopolysaccharide, known to stimulate the innate immune response (via toll-like receptors, as discussed in chapter 6). Particulate air pollution also contains combustion-derived heavy metals such as nickel and vanadium, which can also provoke inflammatory responses.*

[s] *Two-thirds of non-ApoE4 subjects from Mexico City showed amyloid-beta staining, compared to none of the non-ApoE4 subjects from non-air polluted cities.*

From the Smoke Stack to Your Brain
Air Pollution is Linked to Brain Inflammation & Amyloid-Beta Deposition



This diagram represents some of the pathways and mechanisms through which air pollution is thought to have inflammatory and degenerative effects in the brain. The diagram is not intended to be a comprehensive or literal representation of these processes. *(PM=particulate matter)*

pathological marker of Parkinson's disease, was also seen at a relatively high rate (23.5 percent) in young subjects from polluted cities. (See chapter 8.)

The authors concluded that exposure to air pollution is associated with neuroinflammation, an altered innate immune response in the brain, and accumulation of amyloid-beta as well as alpha-synuclein starting in childhood. They suggest that exposure to air pollution should be considered a risk factor for Alzheimer's and Parkinson's diseases. They also note that the ApoE4 gene may increase the risk of developing Alzheimer's disease in an air-polluted environment.[94]

In a separate study, children from highly polluted Mexico City, compared with controls from a low-pollution city, showed a high incidence of cognitive deficits on psychometric testing as well as brain abnormalities in the prefrontal region on MRI.[t] Similar MRI lesions were found in dogs from highly polluted areas. The lesions were associated on postmortem exam with neuroinflammation, ultrafine particulate matter deposition, and gliosis (proliferation of astrocytes, indicating neuronal injury).[95] [u] This suggests that brain inflammation linked with air pollution begins at an early age and is associated with early cognitive impairment. It should be noted that these studies do not tell us which air pollutants are responsible for the observed effects.

Animal studies with allergic[96] [v] or genetically vulnerable[97] [w] mice have demonstrated increased brain inflammation following short-term exposure to concentrated air particulates.[x] Each of these conditions facilitates the breakdown of respiratory epithelium by air particulates or other pollutants. When this barrier is disrupted, inflammatory mediators and particulate matter can more easily pass through to the systemic circulation, thereby facilitating access to the brain.[98]

Inside the brain, inflammatory cytokines activate microglia, a potent agent of neurodegeneration.[99] Elevated cytokines have also

[t] *The MRI abnormalities were white matter hyperintense lesions.*
[u] *These abnormalities were also associated with subcortical vascular pathology.*
[v] *Allergic airway sensitivity in this model was induced by sensitizing the mice to inhaled ovalbumin.*
[w] *Mice that are genetically modified to lose their ApoE gene (so-called ApoE knockouts) have increased oxidative stress.*
[x] *The exposure took place for two to five weeks, lasting 15-20 hours/week.*

been found to increase the expression of an enzyme (COX2) in the capillary lining (endothelium) of the brain, which produces the highly inflammatory prostaglandin, PGE2. Recent evidence links PGE2 with stimulation of amyloid-beta production, providing another possible mechanism that may connect inflammatory particulate air pollution with Alzheimer's disease.[y] [100] [101] [102]

Since PGE2 is derived from omega-6 fatty acids, the relatively high omega-6 fatty acid content of the Western diet (along with the low omega-3 content) may intensify PGE2 production, increasing amyloid-beta formation and the risk of Alzheimer's disease. The influence of omega-3 and omega-6 fatty acids in neurodegenerative disease is discussed further in the nutrition section below.

This evidence is consistent with the established link between air particulates and inflammatory injury to the lung, nose, blood vessels, and heart. These studies suggest that air pollution causes inflammation in the brain[z] and is likely to be contributing to the high prevalence of neurodegenerative diseases in the modern world

This evidence is consistent with the established link between air particulates and inflammatory injury to the lung, nose, blood vessels, and heart.

PCBs and Persistent Organic Pollutants

PCBs are industrial chemicals that were used for many years in a variety of applications, including as paint additives, lubricants, and insulators in electrical equipment. They were banned from production in 1977 in the US because of evidence that they could cause cancer. Subsequently, PCBs were found to interfere with normal brain development and thyroid hormone function.[103] PCBs continue to contaminate the general environment because they are persistent and not easily broken down. Since they are fat soluble and bioaccumulative, they also contaminate the general food supply though levels have been falling. Biomonitoring data from the Centers for Disease Control show that human PCB levels in the general population have also been falling since the ban, though they remain a contaminant of concern.

While there is extensive epidemiology demonstrating the toxicity of PCBs on the developing brain, to our knowledge only three published epidemiologic studies have explored the effects of PCBs on cognitive decline/dementia in older subjects. These studies looked at PCB exposure in three different settings—an oil contamination/poisoning incident (Yucheng), environmental exposure through fish consumption, and a group of occupationally exposed workers. Each study demonstrated

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[y] *PGE2 stimulates amyloid-beta by increasing expression of gamma secretase, one of the enzymes involved in producing amyloid-beta .*

[z] *Particulates and/or inflammation are noted in blood vessels as well as the tissue of the brain.*

an association of adult PCB exposure with dementia/cognitive impairment. While PCB exposures in the oil contamination and occupational studies were relatively high, the exposures in the fish consumption study are closer to those in the general population.

One of these studies tested cognitive abilities in older adults who had been exposed to cooking oil contaminated with PCBs and PCDFs (another persistent organic pollutant) more than 20 years earlier. The study found, among women, significant dose-dependent reductions in attention and memory functions.[aa] [104] Another of these studies found older subjects who regularly consumed Great Lakes fish had impairments in memory and learning compared to controls.[ab] [105] While each of these studies included additional contaminants, the contaminants were different in the two studies and the findings for PCBs were comparable. The third investigation, a retrospective study of over 17,000 PCB-exposed workers showed an excess of dementia mortality among women most highly exposed.[106] [ac] These studies are consistent with prior research showing deficits in memory and learning in children exposed to PCBs before birth or in infancy.[ad] Animal studies as well have shown that exposure to various forms of PCBs reduced learning ability and spatial discrimination among other cognitive impairments.[107-109] The epidemiological studies described are limited by their case-control design. Since they are not longitudinal, prospective studies, they cannot establish when the cognitive decline occurred.

Animal studies as well have shown that exposure to various forms of PCBs reduced learning ability and spatial discrimination among other cognitive impairments.

Several epidemiologic and laboratory (in vitro) studies have linked exposure to PCBs as well as other persistent organic pollutants to inflammation, diabetes,[110] [111] and metabolic syndrome.[112] Low-dose PCBs have also been linked to atherosclerosis[113] and obesity.[114] Since these diseases are themselves risk factors for dementia/cognitive decline, PCB effects on cognitive decline/dementia might be mediated in part through these risk factors, as well as through direct PCB effects on the brain. These studies also provide further evidence that environmental chemicals can increase the risk of other diseases in the Western disease cluster.

The mechanisms whereby PCBs may cause neurodegeneration are not well understood.[115] Some kinds of PCBs interact with the aryl hydrocarbon receptor (AhR), activating a family of enzymes (cytochrome P450 1A1 subfamily) that lead to oxidative stress and

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[aa] *The study was a retrospective cohort investigation involving 162 subjects 60 years of age or older who had been exposed in the Taiwan oil contamination epidemic of 1979.*

[ab] *The cohort study included 101 consumers of Lake Michigan fish, ages 49-86 years of age.*

[ac] *Standardized mortality ratio = 2.04. PCB exposure in this study was estimated by history.*

[ad] *Other developmental effects of PCBs in children include impaired attention and IQ and hyperactivity. (See* In Harm's Way: Toxic Threats to Child Development *p.78)*

free-radical production.[116] Various PCBs have also been linked to inflammatory activation of endothelial cells (a process linked to atherosclerosis),[117] and to the impairment of long-chain fatty acid synthesis.[ae] [118] Since inadequate levels of long-chain fatty acids are implicated in dementia and cognitive decline (see the nutrition section below), the inhibition of long-chain fatty acid synthesis by PCBs may provide another plausible mechanism by which PCBs may promote cognitive decline/dementia. PCBs also affect the function of thyroid hormone, which is implicated in cognitive impairment as well.[119] [120]

Pesticides

A growing body of evidence demonstrates neurologic impacts at lower levels of chronic exposure to neurotoxic pesticides in adults, primarily in the occupational setting.

Pesticides are used extensively in the United States and throughout the world. The licensing of over 18,000 American pesticide products and the application of over two billion pounds of pesticides per year to crops, homes, schools, parks, and forests creates the potential for pervasive human exposures.[121] [122]

Many pesticides exert their killing effects through neurotoxic mechanisms. Historically, most attention was focused on acute effects to humans from relatively large exposures, but in recent years neurological effects from chronic, low-level exposures have been more widely studied in laboratory animals, people who apply pesticides, and the general public. Toxicologists and epidemiologists have been particularly interested in the neurodevelopmental impacts of the organophosphate family of insecticides because of their widespread use and resulting human exposures.[123] Animal and epidemiologic studies of the neurodevelopmental impacts of organochlorines, carbamates, and pyrethroids are less extensive.

Acute high-dose effects of organophosphates include headache, dizziness, nausea, vomiting, papillary constriction, sweating, tearing, and salivation. Severe poisoning may progress to seizures, arrhythmias, coma, and death. Many studies (reviewed in Kamel and Hoppin[124] and others[125]) have documented chronic, lingering symptoms following acute high-dose organophosphate exposure, including cognitive and psychomotor impairment, motor dysfunction, and reduced vibration sensitivity.[126] [127] [128]

Though studies are not fully consistent, a growing body of evidence demonstrates neurologic impacts at lower levels of chronic exposure to neurotoxic pesticides in adults as well, primarily in the

[ae] *Fatty acid metabolism is thought to be impaired due to PCB inhibition of the delta 5 and 6 desaturase enzymes, preventing the elongation of fatty acids.*

occupational setting.[af] [129] These impacts include neurobehavioral performance impairments and sensory, motor, and nerve dysfunction. As noted in Kamel and Hoppin, most (though not all[130] [131]) studies examining cognitive and psychomotor function have documented chronic impairments in association with long-term, lower-dose occupational pesticide exposure. [132] [133] [134] Cognitive domains that are affected include memory, attention, visual-spatial processing, pattern memory, and others. Most of these were studies of organophosphate exposures, though a few examined the organochlorine DDT and fungicides. For example, chronic low-level exposure to fungicides among French vineyard workers increased the risk of poor performance on tests of selective attention and working memory by a factor of 3.5. Tests of associative memory, verbal fluency, and abstraction were similarly impaired.[135]

Several studies have also found an increased risk for Alzheimer's disease or dementia in association with occupational pesticide exposure.

Several studies have also found an increased risk for Alzheimer's disease or dementia in association with occupational pesticide exposure.[136] A six-year prospective study of 1,507 elderly people in France found that a history of occupational exposure to pesticides increased the risk of developing Alzheimer's disease by a factor of 2.39. An increased risk was not seen in agricultural occupations more generally.[137] Another five-year longitudinal, population-based study in Manitoba found that a history of occupational exposure to fumigants/defoliants was associated with a 4.35-fold increased risk of Alzheimer's disease.[138] Several studies have also failed to find associations of pesticide exposure with Alzheimer's disease.[139] [140]

Very few studies have looked for chronic cognitive effects of pesticide exposure in adults outside of the occupational setting. One of these studies conducted in the Netherlands found that gardeners (as well as farmers) had an increased risk of having mild cognitive dysfunction at the outset of the study, as well as an increased risk of developing mild cognitive dysfunction over the three-year course of the study.[141] Another study looking for an association of non-occupational exposure to pesticides (based in part on records of herbicide and insecticide spraying and areas of residence) failed to find a link.[142] The authors of this study noted several methodologic problems – including the use of retrospective exposure assessment and proxy respondents – that might have reduced the ability of the study to recognize an association if it did exist.

[af] *Several issues in research methods contribute to the difficulty demonstrating the cognitive effects of pesticides at lower exposure levels. Notably, accurate prior exposure is especially difficult to determine in the absence of good biomarkers of cumulative exposure for most pesticides. Instead, exposure is generally assessed by history or occupational category. Since such methods typically provide imprecise estimates of exposure, the findings of such studies tend to under-recognize neurotoxic (and other) associations with low level pesticide exposure, (Type II error). This under-recognition of actual associations, it should be noted, does not undermine the validity of any associations that are observed. (Kamel and Hoppin 2004)*

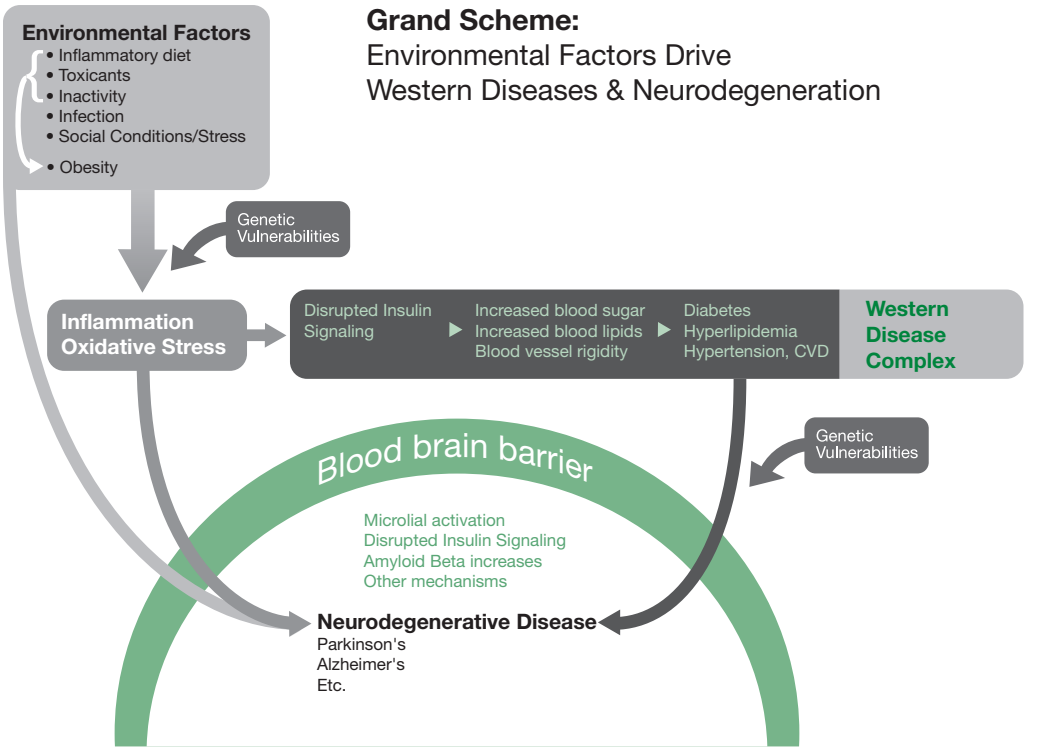
In summary, many but not all studies find that acute high-dose and chronic lower-dose occupational exposures to some neurotoxic pesticides are linked to an increased risk of cognitive decline, dementia or Alzheimer's disease. Data on the effects of chronic non-occupational exposure are too sparse to allow any conclusions. Research attempting to link chronic non-occupational pesticide exposures and cognitive impairment is especially hampered by the difficulty of distinguishing exposed from unexposed subjects (due in part to the lack of long-term exposure biomarkers). This difficulty leads to exposure misclassification, which makes associations with low-dose exposure very hard to identify even if they do exist.

The Western disease cluster and Alzheimer's disease/dementia can be seen in part as consequences of inflammation and the associated disruption of insulin signaling.

Links to Western Disease Cluster and Inflammatory Markers

Substantial epidemiologic evidence suggests that diseases that co-occur in the Western disease cluster are also risk factors for Alzheimer's disease/dementia and cognitive decline. The evidence is strongest for diabetes but is also substantial for midlife hypertension, obesity and elevated total cholesterol.

While each of these diseases is linked to Alzheimer's disease/dementia through multiple mechanisms, inflammatory disruption of insulin signaling provides an emerging common denominator and serves



as a framework as shown in the figure below. (Also see chapter 6 sections on the Insulin and Toll-Like Receptors cascades.) The backbone of this framework consists of inflammatory signaling—triggered by a variety of environmental factors and gene-environment interactions—and the resulting disruption of insulin signaling. Disrupted insulin signaling in turn causes the metabolic and vascular consequences of diabetes: hyperglycemia (elevated blood sugar), hyperlipidemia (elevated blood lipids), and vascular disease. Since inflammation—and the associated oxidative stress—can be transmitted across the blood-brain barrier, systemic inflammation/oxidative stress is also associated with brain inflammation/oxidative stress. These in turn are important drivers of neurodegeneration. Inflammatory disruption of insulin signaling in the brain may contribute to abnormalities that are commonly observed in Alzheimer's disease, namely impairments in glucose metabolism and the synthesis of acetylcholine (a neurotransmitter whose production requires byproducts of glucose metabolism). Thus the Western disease cluster and Alzheimer's disease/dementia can be seen in part as consequences of inflammation and the associated disruption of insulin signaling.

Several large prospective cohort studies found that diabetes was associated with a greater risk of developing cognitive decline and dementia.

Though not all studies are consistent,[ag] an extensive and growing body of epidemiologic literature suggests the association of the Western chronic disease cluster illnesses with increased risks for Alzheimer's disease/cognitive decline. One illustrative study (following over 1,400 middle-aged subjects for more than 20 years on average) found that midlife obesity, high total cholesterol, and elevated systolic blood pressure were all significant risk factors for dementia, each increasing the risk by approximately two-fold. The study also found the risks were additive, increasing the risk for dementia 6.2-fold when all factors were present.[143] Below we focus on studies examining diabetes/hyperglycemia, obesity, metabolic syndrome, and increased inflammatory markers as risk factors for Alzheimer's disease/cognitive decline.

Diabetes/hyperglycemia

Several large prospective cohort studies found that diabetes was associated with a greater risk of developing cognitive decline and dementia. A review of these studies estimated that diabetes increased the risk of Alzheimer's disease by 50–100 percent and of vascular dementia by 100–150 percent.[144] [145] Interestingly, a four-year prospective study of older women found the adjusted risk of developing cognitive impairment is increased not only among diabetics (1.79-fold), but also among those with minimally impaired glucose tolerance,

[ag] *See below for specific examples.*

defined as fasting glucose greater than 110 mg/dL (1.64-fold).[146] Similarly, a large 10-year prospective study of nondiabetic women found that elevated fasting insulin levels also predicted faster decline in scores of verbal memory ability and cognition.[ah 147] Higher C-peptide levels, (indicating increased insulin secretion, which is characteristic of insulin resistance and type II diabetes), were also found to be predictive of cognitive decline in older women without diabetes in the Nurses Health Study.[148] This evidence of a link between hyperinsulinemia and accelerated cognitive decline supports the hypothesis that insulin resistance (associated with inflammation and hyperinsulinemia) is an important contributing cause of cognitive decline and Alzheimer's disease. Other mechanisms by which diabetes/hyperglycemia may increase the risk for Alzheimer's disease/cognitive decline include neuronal damage from increased oxidative stress and advanced glycation end products (amino-sugar compounds that are increased in hyperglycemia and contribute to oxidative stress); reduced acetylcholine production resulting from reduced glucose availability;[149] and insulin effects on amyloid-beta metabolism and vascular disease.[150]

At least three studies have found an association between increased body mass index and cognitive impairment or decline.

Several studies have reported an interaction between diabetes and ApoE4 that increases the risk of developing Alzheimer's disease. One of these studies reported the risk of Alzheimer's disease increased by a factor of 4.58 among diabetics carrying the ApoE4 gene.[151 152]

Obesity

Numerous large prospective epidemiological studies have found midlife obesity to be associated with greater risk of dementia in later life[153-158] (though not all studies are consistent[159 160]). For example, a 27-year prospective study of over 10,000 men and women in the Kaiser Permanente Medical Group found that people who were obese in midlife had a 74 percent increased risk of dementia later in life, while overweight people had a 35 percent increased risk.[161] At least three studies have found an association between increased body mass index (BMI) and cognitive impairment or decline.[162 163] For example, in a study of more than 2,200 healthy workers 32–62 years of age, higher BMI was associated with both lower cognitive scores at baseline and greater five-year cognitive decline.[164] Another cross-sectional study in adults 54–81 years old found the combination of

[ah] *Cognitive status was determined by the Telephone Interview for Cognitive Status.*

greater waist circumference (or BMI) and higher blood pressure was associated with reduced executive function, manual dexterity, and motor speed. [165]

Providing further support for the view that midlife obesity increases risks for cognitive decline, three recent imaging studies showed obesity in middle-aged and older adults was associated with a number of abnormalities in brain structure. Those abnormalities included reduced hippocampal[166] and total brain volumes,[167] increased white-matter hyperintensities[168] (areas of increased signal intensity on MRI exams, thought to reflect small-vessel vascular disease),[169] and temporal lobe atrophy.[170]. Another imaging study found reduced levels of markers of neuron viability (n-acetylaspartate) and membrane metabolism (choline metabolites) in middle-aged subjects with increased BMI. These abnormalities were particularly evident in the frontal lobe, an area of the brain especially prone to damage during aging. These findings underscore concerns that obesity may contribute to abnormalities in brain structure and function in midlife, laying the groundwork for cognitive decline or dementia in later life.[171]

Metabolic Syndrome, Inflammation, and Oxidative Stress

An increase in one or more inflammatory markers is itself a risk factor for cognitive decline/ dementia.

Several[172-175] but not all[176] studies have found metabolic syndrome to be a risk factor for developing Alzheimer's disease/cognitive decline. One of these found metabolic syndrome a significant risk factor specifically in the presence of increased inflammatory markers.[177]

An increase in one or more inflammatory markers is itself a risk factor for cognitive decline/dementia. Fully ten out of eleven large population-based prospective studies have shown positive associations between inflammatory marker elevations and subsequent cognitive decline or dementia/Alzheimer's disease.[178-187] While different studies have found different markers to be associated with increased risk,[ai] the consistent finding of an increase in one proinflammatory marker or another across different populations is notable. The one prospective study that did not find an association used a less sensitive outcome measure (a one-time measure of cognitive function rather than decline across two or more points in time[aj]). This may have reduced the ability of the study to detect an effect if present.[188] [ak] The association of increased inflammatory markers with cognitive decline/dementia is

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[ai] *The different markers found to be associated with cognitive decline/dementia may reflect both differences in study characteristics (experimental design and measurement techniques) as well as potential differences in the populations studied (including different risk factors, nutritional profiles, toxicant exposures, and other poorly identified modifiers of inflammatory response).*

[aj] *Cognitive function is a one-time measure and does not account for baseline cognitive ability.*

[ak] *The study is ongoing and a report on the relation between CRP and cognitive decline is anticipated in the future.*

supported by the very large body of evidence pointing to inflammation as key in the pathogenesis of dementia. This includes histopathology, epidemiology, gene polymorphism studies, and links between inflammatory cytokines and microglial activation and amyloid-beta processing. (See chapter 6.)

While epidemiologic studies have not (to our knowledge) examined the role of oxidative stress in the development of Alzheimer's disease/cognitive decline, an interesting recent study did look at oxidative stress—as indicated by oxidized LDL-cholesterol levels—as a predictor of metabolic syndrome. It followed over 1,800 middle-aged adults for five years and found that oxidized LDL (determined at the outset of the study) predicted the development of metabolic syndrome in a dose-response fashion, with the highest quintile having a 3.5-fold increased risk of metabolic syndrome relative to the lowest quintile. Oxidized LDL also predicted the development of abdominal obesity, elevated fasting glucose, and high triglycerides.[al] [189]

…Social, mental, and physical activity are inversely associated with the risks of Alzheimer's disease/dementia and cognitive decline.

Social, Mental, and Physical Activity

A substantial body of evidence indicates that social, mental, and physical activity are inversely associated with the risks of Alzheimer's disease/dementia and cognitive decline. This includes long-term human observation and controlled animal studies. The animal studies provide important corroborating evidence for the human observational studies, which are subject to certain difficulties that we will explain.

A body of relevant animal research literature has emerged in the area of "environmental enrichment." This research demonstrates the relationship of cognitive performance—as measured, for example, by performance on the Morris water maze, a test of memory—to variations in the cage environment. The cage environment is varied by changing the number of objects available for exploration or the number of animals in the cage. Two important and consistent findings have emerged from this literature. First, and not surprisingly, rodents learn and remember better in an enriched environment. Second, neurogenesis (the creation of new nerve cells) is increased in an enriched environment, specifically in the hippocampus. One of the mechanisms reported to account for this remarkable finding is increased synaptic and dendritic growth. Other preliminary, as yet

[al] *Being in the highest (vs. lowest) quintile for oxidized LDL increased the risk of having abdominal obesity, elevated fasting glucose, high triglycerides, and metabolic syndrome by a factor of approximately 2.3.*

unreplicated findings include increases in brain-derived nerve growth factor and alterations in amyloid-beta levels.[190 191 192]

Human studies show analogous findings in the areas of social, physical, and mental activity. A recent review of 15 longitudinal studies found an increased risk of cognitive decline with reduced social networks (5 of 7 studies) and physical inactivity (6 of 7 studies). Increased dementia risk was also found in relation to reduced social networks (6 of 7 studies). While all studies were assessed as methodologically sound, the possibility that reduced social, mental, and physical activity is itself an expression, rather than a cause, of early dementia cannot be excluded.[am 193 194] Thus, animal studies showing the benefits of environmental enrichment provide important corroborating evidence. Specific findings of human studies include the following:

Engaging in leisure time physical activity at least twice a week in midlife was associated with a greater than 50 percent reduction in risk of dementia/ Alzheimer's.

- Substantial reductions were seen in the rate of cognitive decline among subjects with extensive social networks and social engagement, in a group of over 6,000 African-American and Caucasian elders followed for over five years.[195] (The rate of cognitive decline was reduced 39% in subjects with high social network ratings, and 91% in those with high social engagement ratings.)
- Engaging in leisure time physical activity at least twice a week in midlife was associated with a greater than 50 percent reduction in risk of dementia/Alzheimer's disease. This group was followed for more than 20 years.[196]
- Cognitive inactivity was associated with a 2.6-fold increased risk of developing Alzheimer's disease, a higher incidence of mild cognitive impairment, and more rapid decline in cognitive function in a group of more than 700 elders followed for up to 5 years.[197]

A growing number of studies have begun to clarify one mechanism in particular that may account for much of the pervasive benefits of exercise—for cognitive function as well as for cardiovascular disease, diabetes, and other components of the Western disease complex. In brief, these studies suggest that exercise transiently increases reactive oxygen species (free radicals), and then strongly up-regulates antioxidant capacity. The net effect is that people who exercise regularly have reduced ongoing levels of oxidative stress and inflammatory burden.[198-200]

[am] *The technical term for this problem is reverse causation.*

Psychosocial Stress

Social, mental, and physical activity also help moderate the effects of psychosocial stress—broadly defined as a variety of states associated with distress, namely depression, anxiety, social isolation, chronic life stress, personality traits, and other individual or community characteristics.[201] Psychosocial stress is well established as a risk factor in cardiovascular disease. While the role of psychosocial stress in dementia/cognitive decline is complex and incompletely understood, a growing body of evidence suggests an emerging key role in the development of dementia/cognitive decline.

Psychosocial stress is well established as a risk factor in cardiovascular disease.

Though relatively few epidemiologic studies have looked at the role of stress in neurodegenerative disease, the studies that do exist suggest that psychosocial stress has an important influence in the development of cognitive decline and dementia. Numerous studies suggest that depression is a risk factor for later development of Alzheimer's disease.[202] [203] Though some studies suggest depression is a very early (prodromal) symptom of Alzheimer's disease rather than a risk factor for the illness,[204] [205] a recent meta-analysis of 20 studies found that a history of depression approximately doubled the risk for the later development of Alzheimer's disease.[an] [206] Similarly, recent prospective cohort studies found the tendency to experience psychological distress was associated with a tenfold increased risk in episodic memory decline[ao] [207] and a 2.7-fold increased risk of developing Alzheimer's disease.[208] An anatomic basis for the association of stress and Alzheimer's disease/cognitive decline is suggested by observations that major depression and post-traumatic stress disorder are associated with smaller hippocampal volume,[209] [210] though not all studies are consistent.[211]

A substantial body of work describes multiple mechanisms linking stress with increased risk of Alzheimer's disease/cognitive decline. One key mechanism is provided in the hypothalamic-pituitary-adrenal (HPA) axis—or "stress circuit."[ap] This axis links depression, anxiety, or other stressors with a cascade of events involving the hypothalamus and pituitary in the brain (which increase corticotropin-releasing hormone [CRH] and adrenocorticotropin [ACTH], respectively) and the adrenal glands (which increase cortisol, epinephrine, and norepinephrine). These hormones increase blood pressure, heart rate, and blood

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[an] *The odds ratio was 1.9 in cohort studies, and 2.03 in case control studies.)*

[ao] *The 90th and 10th percentiles for being distress-prone were compared.*

[ap] *The HPA Axis hypothesis was developed by Drs. George Chrousos, Chief of Pediatric and Reproductive Endocrinoology at the National Institute of Child Health and Human Development, and Philip Gold of the Clinical Neuroendocrinology Branch at the National Institute of Mental Health. The theory is based on a large body of observational and laboratory data involving people and animals.*

sugar, among other effects. In addition, the sympathetic nervous system and a variety of other basic functions—including the immune and reproductive systems, growth, and gastrointestinal tract—are affected. Normally cortisol acts through a negative feedback loop to reduce CRH production, shutting down the stress activation after the threat has passed. In the presence of chronic stress, however, these hormones and systems are continually activated, contributing to risks for high blood pressure, elevated blood lipids, atherosclerosis, impaired growth in children, and reproductive dysfunction, among other effects.[212]

A variety of studies support a link between the HPA axis and Alzheimer's disease/cognitive decline. Animal[213] and/or human studies[214] have shown stressful experience or depression was associated with increased levels of adrenal corticosteroids, and that these hormones can damage the hippocampus (which has a high concentration of corticosteroid receptors[215]) and worsen damage from other neurological insults.[216] Some studies suggest that elevated blood cortisol levels are related to clinical progression of dementia/cognitive impairment.[217] [218] Further, stressful experience and depression themselves may be associated with structural changes in the hippocampus and impaired forms of learning and memory.[219] Providing additional support, recent studies in an Alzheimer's mouse model showed that isolation stress over three months increased amyloid-beta levels in brain interstitial fluid by 84 percent. Acute restraint stress increased amyloid-beta levels within hours, an effect that was mediated by CRH.[220] Isolation stress in this model has also been associated with impairment in memory function, decreased neurogenesis, and greater amyloid-beta deposition.[221]

Psychosocial stress has also been linked with elevated cytokine production.

Endothelial dysfunction provides another mechanism linking psychosocial stress with cardiovascular disease in animals and humans.[222] [223] Since vascular disease associated with endothelial dysfunction increases risks for dementia, the linkage of psychosocial stress to endothelial dysfunction may also contribute to cognitive decline/dementia.

Psychosocial stress has also been linked with elevated cytokine production. Several studies in people show that chronic stress increases age-related proinflammatory cytokine production.[224] One of these showed that the rise in IL-6 cytokine levels over a six-year period was four times greater in a group of 119 stressed spouses caring for partners with Alzheimer's disease than in non-stressed controls.[225] Another cross-sectional study of 43 older adults showed a similar relationship of higher cytokine levels in association with greater depressive symptoms.[226] Interestingly, higher ratios

of omega-6:omega-3 fatty acids in the blood increased the association of depression with cytokine levels in this study. In other words, the combined effect of depressive symptoms and higher omega-6:omega-3 ratios increased proinflammatory cytokine production beyond the effect of either variable alone.[aq] A similar pro-inflammatory effect of higher omega-6:omega-3 ratios was seen in the effects of exam stress on cytokine production (in stimulated blood specimens) in a group of 27 university students.[227] These and other studies underscore concerns about the potential aggravating role that high omega-6:omega-3 ratios in the American diet may play in promoting proinflammatory cytokine elevations in high-stress conditions.

Animal data also support the link between psychosocial stress and elevated cytokine production. Rats, for example, exposed to tail-shock stress prior to injection with LPS produced more proinflammatory cytokines, or produced them more rapidly, than did unstressed rats.[228] Studies in stressed mice and in cell culture identified noradrenalin (also known as norepinephrine) as the factor activating—in a dose- and time-dependent fashion—NFkB expression. This identifies a specific pathway by which stress (via sympathetic nervous system and HPA axis activation) may promote mononuclear cell activation—contributing to the development of cardiovascular and other chronic inflammatory diseases.[229]

Although studies have not yet—to our knowledge—examined the role of stress-induced cytokine elevations in the development of dementia/cognitive decline, a substantial body of prospective studies shows a consistent association of elevated cytokines with subsequent dementia/cognitive decline. (See "Metabolic Syndrome, Inflammation, and Oxidative Stress" above.)

Very few long term clinical studies have examined the potential effects of stress reduction on chronic diseases. One three-year randomized controlled clinical trial showed impressive benefits of stress management on important markers of cardiovascular risk in subjects with established ischemic heart disease. In addition to showing reduced depression and distress, subjects randomly selected to practice stress reduction had reduced ischemia and improved cardiac function during mental-stress testing, improved endothelial function (as measured by flow-mediated dilation) and enhanced autonomic activity (as indicated by improved heart rate variability and baroreflex sensitivity).[230 ar] Relaxation techniques have also been shown to reduce blood

Relaxation techniques have also been shown to reduce blood pressure by 5–10 mm in some subjects.

[aq] *Together these two factors accounted for accounted for 18% of the IL-6 and 40% of the TNF-*α*variance.*

[ar] *The stress management program consisted of 1.5 hours per week of instruction in stress management skills, muscle relaxation, and imagery techniques for 16 weeks.*

pressure by 5–10 mm in some subjects.[231] In addition, numerous uncontrolled, non-randomized, short term pilot studies suggest that a variety of stress reduction techniques (yoga, mediation, mindfulness based stress reduction) may be beneficial, and merit further investigation. These studies found improvements in various cardiovascular, immune, endocrine, autonomic and psychometric indicators after short term use of stress reduction techniques. Two large randomized trials did not find a benefit of stress management on cardiac morbidity and mortality. This may be due to the fact that the stress management did not reduce emotional distress.[232] [233]

In summary, psychosocial stress, an established risk factor for cardiovascular disease, is increasingly linked to cognitive decline/dementia. Chronic activation of the HPA axis, or stress circuit, appears to play a key role in mediating this risk, and is associated with hippocampal damage, elevated amyloid beta levels and dementia. Stress and HPA activation are also associated with increased cytokine production, which in turn has been associated with cognitive decline/dementia in a large body of studies. Clinical intervention studies are difficult to design and conduct, and few long term randomized controlled trials have been done to examine the effects of stress reduction on chronic illnesses of the Western disease complex. None the less, one three-year randomized controlled trial showed impressive benefits of stress management on important markers of cardiovascular risk in subjects with established ischemic heart disease.

Socioeconomic Status and Education

The relationship between socioeconomic status and dementia risk is complex and data are somewhat inconsistent. Difficulties arise because lower socioeconomic status is often associated with poor nutrition, lifetime exposures to environmental pollutants, less education, stress, and sometimes unhealthy behaviors. Most, but not all, studies show that less education is associated with an increased risk of dementia/Alzheimer's disease. One study shows that the higher risk of dementia associated with less education is independent of unhealthy lifestyle factors, such as smoking.[234] When education and socioeconomic status are each evaluated, less education seems to be the more important determinant of risk.[235] The combination of low socioeconomic status and elementary school–only education increased the risk of Alzheimer's disease threefold compared to people with high socioeconomic status and higher education. Some data also show that clinical symptoms of dementia appear earlier

in people of lower socioeconomic status when compared to people of higher socioeconomic status, including those with more objective evidence of brain volume loss and pathology on imaging.[236] These findings suggest that the combination of lower socioeconomic status and less education is a combination that may accelerate the onset of dementia/Alzheimer's disease and that increased brain reserve, associated with more education, may be somewhat protective.

Nutritional Factors

The critical importance of dietary factors is now recognized in the prevention and treatment of diabetes (particularly type II) and cardiovascular disease. [237] [238] Similarly, dietary factors are emerging as critical factors in cognitive function and brain aging. [239-241] Not unexpectedly, the dietary factors that reduce risks of diabetes and cardiovascular disease likewise likewise appear to reduce risks for cognitive decline/dementia.[242] While many studies have focused on single nutrients, combined effects of various nutrients and broad dietary patterns are also vitally important. This was illustrated in one epidemiologic study that found if only one "good" dietary habit—such as either omega-3 fatty acid or fruit/vegetable consumption—was present, it did not provide protection against the development of dementia. However, if these two "good" dietary habits were present, the risks were significantly reduced (hazard ratio 0.72). [243]

Difficulties Studying the Impacts of Nutritional Factors in Cognitive Decline/Dementia

Scientific studies examining the impacts of nutrition on disease risks are difficult to design and implement in a way that produces valid information. As a result, the existing literature is often ambiguous. Long ago, the field of nutritional science adopted the habit of studying the diet as a collection of nutrients that could be manipulated and examined one by one rather than as a complex mixture of relationships. Perhaps this approach gained currency when single vitamin deficiencies were discovered to cause specific diseases and fortification programs reduced or eliminated the problem. But whatever the reasons, this approach is also consistent with the general reductionist approach to science that dominated during the 20th century. More recent epidemiologic studies are beginning to study the impacts of various patterns of eating rather than of single foods or nutrients.

Whether focused on single nutrient or dietary patterns, clinical nutrition studies are inherently difficult for a number of reasons. For example, dietary exposure to various nutrients is usually estimated mainly through the use of food frequency questionnaires, which have substantial uncertainties. While biomarkers (such as omega-3 levels in the blood) may provide more reliable evidence of dietary consumption, such biomarkers of consumption are usually unavailable or unaffordable. Another problem is that the consumption of a given food (such as fish) also entails not eating other foods (such as fast food). It can be difficult to differentiate the effects of what is being eaten from the effects of what is not being eaten. Another difficulty is that long latencies for development of dementia require long duration for prospective studies, further driving up the cost of the study. Further, since food choices are often part of a pattern of broader healthy choices, it may be difficult to control for residual confounding by these other choices.

And finally, the gold standard for evidence—the randomized, controlled clinical trial—is virtually impossible to conduct, in part because it is very difficult to blind subjects to what they're eating. In addition, long-term dietary interventions are inconvenient and compliance requires an extraordinary effort on the part of subjects. Thus, there is a notable lack of long-term nutritional intervention studies in the area of dementia/cognition—as in other areas as well.

Consequently, the understanding of nutritional factors in cognition must derive from other forms of inquiry—human observation, brief clinical investigations, and animal intervention studies. Such data have allowed important conclusions to be drawn in the areas of diabetes and heart disease that are key to the prevention of these diseases, despite the obstacles to conducting long-term nutrition intervention studies.

The difficulty of defining and measuring dietary patterns and the lack of studies looking at multiple nutrient interactions limit the current database. Nonetheless, several general conclusions regarding nutritional influences of cognitive decline are supported by existing data. Here we briefly summarize some of the key conclusions.

Lipids

Not unexpectedly, the dietary factors that reduce risks of diabetes and cardiovascular disease likewise appear to reduce risks for cognitive decline/dementia.

Lipids are important building blocks in the brain. They provide the key constituent of nerve cell membranes as well as the substrate for myelin that wraps nerve axons, providing insulation to preserve nerve impulses as they flow from one cell to another. Lipids are also key players in immune system function. In particular, saturated fatty acids activate, and polyunsaturated omega-3s reduce, the innate immune response (via Toll-like receptors, as discussed in chapter 6). In addition, omega-6 and omega-3 fatty acids modulate another major driver of inflammation, the eicosanoid system (prostaglandins, thromboxanes, and leukotrienes). With brain composition and immune function being intimately linked to the body's lipid profile, it is not surprising that dietary lipids influence cognitive function and aging.

In general, a large body of studies, with a few exceptions, [244] [245] shows that saturated fat consumption is associated with increased cognitive decline/dementia, while omega-3 fatty acids are associated with reduced risks. This is discussed in greater detail below.

Saturated Fat and Cholesterol

Both human epidemiologic studies and controlled animal dietary experiments implicate saturated fat in impaired cognition and/or dementia. Many prospective dietary studies have shown that increased dietary saturated fat consumption increased the risk of dementia by as much as two or three fold.[246-255] One prospective study (Rotterdam) showed increased risk with saturated fat after two years of follow-up, though not after six years.[256] Animal studies also implicate saturated fat. For example, young rats fed a high-saturated-fat diet for three months showed impaired learning and memory relative to those fed low-fat chow. No impairment occurred with high poly- or mono-unsaturated-fat diets.[257]

Diets with high saturated- or trans-fat content adversely affect serum cholesterol,[258] increasing LDL and decreasing HDL.[259] [260] Several prospective epidemiologic studies have shown that elevated midlife serum cholesterol levels are a risk for Alzheimer's disease/cognitive decline.[261-262] One study of 444 Finnish men, for example,

found that elevated blood cholesterol in midlife was associated with a threefold increased risk of developing Alzheimer's disease in late life.[263] Studies looking at cholesterol levels in later life have generally not found an association with Alzheimer's disease/dementia risk.[264] This may be due to alterations in cholesterol metabolism and diet that occur early in the onset of dementia.[265-267]

Dietary and serum cholesterol may promote cognitive impairment by increasing amyloid-beta generation and deposition.[268-269] This is illustrated in a study in which a high-fat/high-cholesterol diet worsened Alzheimer's pathology, including amyloid-beta accumulation, in an Alzheimer's mouse model. Plasma and central nervous system total cholesterol were strongly correlated with amyloid-beta.[270]

Many prospective dietary studies have shown that increased dietary saturated fat consumption increased the risk of dementia by as much as two or three fold.

Omega-3 and Omega-6 Fatty Acids

Omega-3 and omega-6 fatty acids are both essential but their biological effects differ. Omega-3 fatty acids have anticlotting and anti-inflammatory properties.[271] Their essential role in infant brain development has been recognized for decades. Only more recently have their effects on brain aging been explored. In laboratory studies, omega-3s have been shown to benefit learning and memory in rodents. Remarkably, omega-3s have also been shown to have striking benefits in older rodents. For example, DHA (a long-chain omega-3 fatty acid) supplementation in aged rats improved memory-related learning, hippocampal fatty acid levels, and synaptic function, and reduced hippocampal oxidative markers.[272 273] Another study showed that administering DHA to aged Alzheimer's-prone rats reduced total amyloid-beta by more than 70 percent compared with low-DHA or control chow diets. Image analysis of brain sections showed plaque burden was reduced by more than 40 percent.[274]

A large body of human epidemiologic studies (11 of 13 prospective and 3 of 3 cross-sectional studies) indicate that dietary omega-3s and/or fish consumption (the major source of long-chain omega-3 fatty acids) substantially reduce the risk of Alzheimer's disease/cognitive decline.[275-289] For example, a recent Minneapolis study of over 2,200 men and women aged 50–60 years found that intake of long-chain omega-3s (DHA and EPA) was associated with less decline in verbal fluency (odds ratio 0.74). Subjects with hypertension and dyslipidemia showed greatest benefit, with the risk of verbal fluency decline reduced by about half (odds ratio approximately 0.5).[290] In addition, a double-blind, randomized, placebo-controlled clinical intervention study showed a mild positive effect of omega-3

Dietary omega-3s and/or fish consumption substantially reduce the risk of Alzheimer's disease/cognitive decline.

fatty acids on the rate of cognitive decline in patients with very mild Alzheimer's disease.[291]

Interestingly, a recent large prospective study[as] found that the use of omega-6 oils—that was not offset by use of omega-3-rich oils or fish—more than doubled the risk of dementia (hazard ratio 2.12). This effect was not seen among ApoE4 carriers.[292] Such an effect would be consistent with the role of omega-6 fatty acids as substrate for inflammatory mediators (eicosanoids) that are implicated in neuroinflammation. The potential for excessive omega-6 fatty acids to interfere in omega-3 fatty acid cognitive benefits is illustrated in an animal study showing that the reversal of learning impairments[at] in omega-3-deficient rats occurred only when omega-3s were restored to the diet and omega-6s were reduced. Restoring omega-3s alone (without reducing the high intake of omega-6 fatty acids) did not reverse the learning impairment.[293]

Fruits and Vegetables

Though relatively few human epidemiologic studies have been done, most indicate that high intake of fruits and vegetables is associated with decreased risks of cognitive decline.[294-300] This association is further supported by studies in animal models showing that fruit and vegetable extracts protect against cognitive and brain neuropathology from dietary oxidative stress in aged rodents.[301 302] The benefits of fruits and vegetables are thought to be due to various antioxidant and bioactive components including vitamins E and C, carotenoids, flavonoids, and other polyphenols.[303]

Antioxidants

Evidence from animal and laboratory studies shows that vitamin E and other antioxidant nutrients reduce oxidative and inflammatory damage.[304] Limited prospective studies on the effects of food intake of vitamin E and vitamin C in humans, however, are inconsistent. Studies on the effects of vitamin C and E supplements have generally been negative. For vitamin E, this may be due in part to the fact that vitamin E supplements have traditionally contained only one of at least eight naturally occurring forms of tocopherol.[305]

Polyphenols

Plant polyphenols are a large class of natural antioxidants suspected to be responsible for some of the health benefits of fruit and vegetable

[as] *The study followed over 8,000 French subjects for approximately 3.5 yrs.*
[at] *Learning was tested in a brightness-discrimination learning test.*

consumption. In addition to antioxidant characteristics, polyphenols also demonstrate a variety of neuroprotective properties in animal and in vitro studies. The polyphenol curcumin, which is contained in the spice turmeric, for example, has been shown to inhibit amyloid-beta aggregation and fibril formation in vitro. When fed to aged Alzheimer-prone mice with advanced amyloid accumulation,[au] curcumin reduced levels of amyloid and plaque burden.[306] Similarly, blueberry extracts, highly concentrated with acanthocyanin polyphenols, have been shown to prevent and even reverse age-related deficits in neuronal signaling and cognition in rats.[av 307 308] Blueberry supplementation was also shown to increase neurogenesis and improve memory performance in aged rats.[309] Polyphenols also act as free radical scavengers, regulate nitric oxide, inhibit cell proliferation, and reduce the immobilization of leukocytes.[310]

Studies ... indicate that high intake of fruits and vegetables is associated with decreased risks of cognitive decline.

Polyphenols can be subdivided into 10 or more classes based on chemical structure.[aw] Over 6,000 members of the flavonoid family alone have been identified,[311] including acanthocyanins, found in high concentrations in blueberries;[312] resveratrol, found in red wine; and catechins, in green tea and some cocoa and chocolate.

While the scarcity of studies does not yet permit conclusions to be drawn, limited laboratory, animal, and human epidemiologic evidence is highly suggestive that dietary polyphenols have a significant neuroprotective influence.

Very few epidemiologic studies have looked specifically at the possible influence of polyphenols in cognitive decline/Alzheimer's disease. Two studies in the French PAQUID cohort, with over 1,300 participants, did find consistent flavonoid associations with improved cognition.[313 314] Specifically, the studies found that flavonoid intake was associated with better cognitive function at baseline. At five years, the adjusted relative risk of dementia was approximately cut in half for subjects in the two highest tertiles of flavonoid intake compared to the lowest. And at 10 years follow-up, subjects in the lowest quartile of flavonoid intake had lost an average of 2.1 points on the Mini-Mental State Exam, compared with a loss of 1.2 points among those in the highest quartile of flavonoid intake.

A recent review of prospective cohort studies[315] found that 7 of 12 studies showed flavonoid intake associated with reduced risk of coronary artery disease. One study in Welsh men[316] found the opposite

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[au] *Tg2576 mice, (carrying a mutant form of amyloid precursor protein), were raised on a Purina chow diet with 500 ppm curcumin added, until the age of 22 months.*

[av] *Some, though not all, improvements were also demonstrated in rats receiving spinach and strawberry extracts, also high in polyphenols.*

[aw] *All plant poyphenols share the chemical structural feature of a central aromatic ring with one or more hydroxyl groups.*

In addition to antioxidant characteristics, polyphenols also demonstrate a variety of neuroprotective properties in animal and in vitro studies.

association, though the results did not achieve statistical significance (p=0.1) and may have been influenced by methodology problems.[ax]

Vitamins B6, B12, Folate, and Homocysteine

Homocysteine, an amino acid, is the byproduct of the metabolism of other amino acids (specifically the conversion of methionine to cysteine). While extreme elevations of homocysteine are caused by a rare genetic disorder (homocystinuria), mild-to-moderate elevations found in 5–7 percent of the population are most commonly caused by dietary deficiencies of folate, B12, and B6,[ay 317 318] vitamins that are essential for homocysteine metabolism. Moderate elevation of homocysteine is recognized as an independent risk factor for cardiovascular, cerebrovascular, and venous thromboembolic disease, (heart attacks, strokes and blood clots). The risks associated with homocysteine elevations, however, appear to be less than those associated with traditional cardiovascular risk factors.[319-321]

Lowering homocysteine through vitamin supplementation has not been shown to be of benefit for cardiovascular or venous thromboembolic disease.[322] Several large controlled clinical trials are now underway to assess the benefit of folate, B12, and B6 supplementation in preventing cardiovascular disease.

Evidence linking homocysteine elevations (and/or inadequate intake of folate, B12, and B6) to dementia/cognitive decline is mixed but increasingly suggestive. One recent large observational study of over a thousand older subjects found elevated plasma homocysteine a strong risk factor for the development of dementia and Alzheimer's disease.[323] Another large observational study found that higher dietary folate intake (which reduces homocysteine) was associated with reduced risk of developing Alzheimer's disease. Specifically, those in the highest quartile of folate intake showed half the risk of developing Alzheimer's disease (compared to lowest quartile).[324] These studies were notable for lasting 8 and 6 years. Two shorter observational studies—lasting 2.7 and 3.9 years—did not see an association between dietary folate/B12/B6 and incidence of Alzheimer's disease, perhaps because the observation time was too short to allow the effect to be seen.[325 326] Further support for an association of homocysteine levels with cognitive decline is provided by a recent large cross-sectional study showing higher plasma homocysteine

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[ax] *The result was thought potentially due to residual confounding, and/or possibly to the British habit of adding milk to tea, (the major source of flavonols in this population), inhibiting the absorption of flavonols.*

[ay] *Additional causes of mild-moderate homocysteine elevations include genetic defects, chronic medical conditions, pharmaceuticals, and other factors.*

levels are associated with silent brain infarcts and smaller brain volume on MRI in healthy, middle-aged adults.[az] [327]

Recently, clinical intervention studies have begun to test the influence of the relevant B vitamins (and the resulting homocysteine lowering) on cognitive function over time. Results of these early intervention studies—which have been limited by modest duration and sample sizes—have been mixed. [328-331] However, a recent trial with a larger subject number and longer duration [ba] found that folate supplementation was associated with a 26 percent reduction in plasma homocysteine and improved cognitive function[bb] compared to the placebo group.[332] Additional intervention studies will be needed to confirm this emerging role of homocysteine in cognitive decline and the role of folate supplementation in preventing this increased risk.

Rich food sources of folate include legumes (lentils, chick peas), green leafy vegetables (spinach, turnip greens, lettuces), sunflower seeds, and certain other fruits and vegetables. Some breakfast cereals are fortified with folic acid. The USDA provides a database of selected food sources of folate (and other nutrients) which can be found at the USDA National Nutrient Database for Standard Reference.

Dietary Patterns: The Mediterranean-Type Diet

As mentioned above, there is increasing interest in the influence of dietary patterns rather than single nutrients on a variety of health concerns. A focus on dietary patterns can capture complex interactions among many components that are difficult or impossible to see when looking at one or two nutrients individually.[333]

Interest in one such pattern, the Mediterranean diet, was first kindled by the work of Ancel Keys in the 1950s, who pointed out the very low rates of coronary disease and some cancers and long life expectancy on the island of Crete, despite high fat intake in the diet.[bc] While there is no single Mediterranean diet, the term is generally used to refer to diets characterized by high intake of vegetables, legumes, fruits, whole cereals, fish, nuts, and unsaturated fatty acids (especially olive oil); low-moderate dairy products; low saturated fats and meat; and regular moderate ethanol, primarily in the form

Interest in the Mediterranean diet was first kindled by the work of Ancel Keys in the 1950s, who pointed out the very low rates of coronary disease and some cancers and long life expectancy on the island of Crete, despite high fat intake in the diet.

[az] *The study included over 1900 subjects in the Framingham Offspring Study in a cross-sectional investigation.*

[ba] *Additional techniques included more sensitive outcome measures (testing specific cognitive domains rather than global performance), and statistical clustering of multiple raw test scores (to reduce variability of individual tests and improve the "robustness" of the measurements).*

[bb] *Improvements in cognitive function were found in memory, information processing speed, attention and concept shifting (similar to executive function), referred to by the author as sensorimotor speed.*

[bc] *It is now acknowledged that the benefits attributed to the Mediterranean diet in the Keys studies may have been influenced by poorly controlled co-variants such as physical activity.*

Adherence to the Mediterranean diet was associated with a risk of Alzheimer's disease that was reduced by more than a third.

of wine with meals. The benefits of the Mediterranean diet have generally been attributed to the combined effects of high content of antioxidants (in olive oil, vegetables, and fruits), high omega-3 fatty acids, low saturated fat,[334] low glycemic index, and high fiber content (due to reliance on whole rather than processed grains). We use the term Mediterranean-type diet here to refer to other diets as well, such as the "prudent" diet, that share most of the above characteristics.

The Lyon Heart Study was the first clinical trial showing compelling health benefits—specifically a 73 percent reduction in recurrent heart attacks and a 70 percent reduction in total mortality in a group of over 600 patients randomly assigned to a Mediterranean-type diet (vs. conventional medical dietary advice) following a heart attack.[335] Subsequently, a large body of observational and intervention studies (though not all studies) have shown benefits of a Mediterranean-type diet on the spectrum of diseases in the Western disease cluster. Beneficial effects have been shown for diabetes,[336] [337] obesity, metabolic syndrome,[338] chronic inflammation,[339] cardiovascular disease, and abnormal blood lipids.[340]

Several recent prospective studies have also demonstrated benefits of the Mediterranean diet in reducing cognitive decline[341] and Alzheimer's disease. One study following over 2,000 New York residents found that adherence to the Mediterranean diet over four years was associated with a risk of Alzheimer's disease that was reduced by more than a third.[bd] [342] Another prospective study of 192 community-living individuals with Alzheimer's disease found that those in the highest third for adherence to the Mediterranean diet had a markedly lower mortality risk (OR 0.27) as well as nearly four years longer survival, relative to those in the lowest third for adherence.[343]

Ethanol

Mild-to-moderate alcohol consumption has been recognized to have a protective effect against cardiovascular disease in middle-aged and older adults.[344] Similarly, a growing body of evidence suggests that light-to-moderate alcohol consumption is protective against dementia, [345] though high levels of alcohol intake and alcoholism itself are associated with cognitive dysfunction[346] and dementia. The alcohol-dementia association may also be complicated by other factors (including smoking, head trauma, and vitamin, antioxidant, and dietary deficiencies).[347]

Two large cohort studies showed substantial risk reduction for dementia (hazard ratio = 0.46-0.58) with light-to-moderate alcohol consumption.[348] [349] A study of over 11,000 US nurses also showed that consumption of one drink per day or less was associated with a

[bd] *OR= 0.6, comparing the most to least adherent thirds of the population*

reduced risk of cognitive impairment, (with relative risk compared with abstinence = 0.85).[350] A recent meta-analysis of 23 studies concluded that limited alcohol intake in earlier adult life may be protective against the development of dementia in later life. The relative risk for dementia and Alzheimer's disease was approximately 0.6.[351]

The ApoE4 gene appears to modify—and potentially even reverse—the alcohol benefit. Several (though not all[352]) observational studies suggest that individuals carrying the ApoE4 gene do not benefit from mild-to-moderate alcohol intake.[353 354] In a study of over 1,300 French subjects (59–71 years old) followed for four years, non-ApoE4 carriers who reported drinking two or more glasses of alcohol per day had a roughly 50 percent decrease in the risk of cognitive deterioration compared to nondrinkers. In contrast, those who carried at least one ApoE4 gene showed a positive association between alcohol consumption and cognitive deterioration.[355]

Two studies showed a reduced risk of dementia only with wine consumption[356 357] while others found no difference in risks according to beverage type.[358 359]

Mechanisms by which alcohol may exert protective effects are not clearly established, though the benefits of red wine consumption are thought to be due in part at least to the polyphenol resveratrol. Alcohol is also a modulator of fatty acid metabolism, specifically promoting higher levels of long-chain omega-3 fatty acids,[360 361] which are associated with reduced risk for cognitive decline/Alzheimer's disease. It has been speculated that a "fish-like effect of moderate wine drinking" might partly explain the protective effects of wine drinking against cardiovascular disease.[362] If so, it is possible that such an effect might play a role in the neuroprotective effect of limited alcohol consumption.

A growing body of epidemiological evidence suggests an association between occupational exposure to extremely low frequency magnetic fields and dementia/ Alzheimer's disease.

Electromagnetic Field Exposure

A growing body of epidemiological evidence suggests an association between occupational exposure to extremely low frequency magnetic fields (ELF-MF) and dementia/Alzheimer's disease. ELF-MF are generated by electric-powered equipment,[be] among other sources. They are part of a spectrum of electromagnetic waves that run from gamma rays at the highest frequency end, through x-rays, ultraviolet rays, visible light, infrared radiation, microwaves, radio waves, very low frequency, and extremely low frequency waves at the lowest end. Most research has focused on long-term health effects in workers exposed to magnetic fields typically encountered by electric power installers and repairers, power plant operators, electricians, electrical and electronic

[be] *Power-frequency fields are typically 50–60 Hz.*

equipment repairers, telephone line technicians, seamstresses, tailors, welders, carpenters, or others who operate electrical equipment.[363] [364]

A recent systematic review and meta-analysis[365] found a 1.6 to twofold increased risk[bf] for those occupationally exposed to electromagnetic fields, using 14 published epidemiologic studies with adequate methodology.[bg] Another review prepared for the BioInitiative Working Group found six out of seven epidemiologic studies[bh] generally positive for an association between ELF-MF and Alzheimer's disease, with only one study failing to find an association.[366]

...this evidence is suggestive that extremely low frequency magnetic fields could potentially increase risk for Alzheimer's disease by reducing brain levels of neuroprotective melatonin.

One of the mechanisms proposed to mediate the increased risk of Alzheimer's disease with ELF-MF exposure is reduced melatonin production. Numerous epidemiologic studies (11 of 13 reviewed in the BioInitiative Working Group study) found that high ELF-MF exposure was associated with reduced melatonin production in occupational and residential settings. [367] Melatonin has been shown to be neuroprotective in a number of animal and in vitro studies. Melatonin effects include inhibition of amyloid beta neurotoxicity, oxidative stress in transgenic mouse models of Alzheimer's disease, and proinflammatory cytokine production induced by amyloid-beta in rat brains.

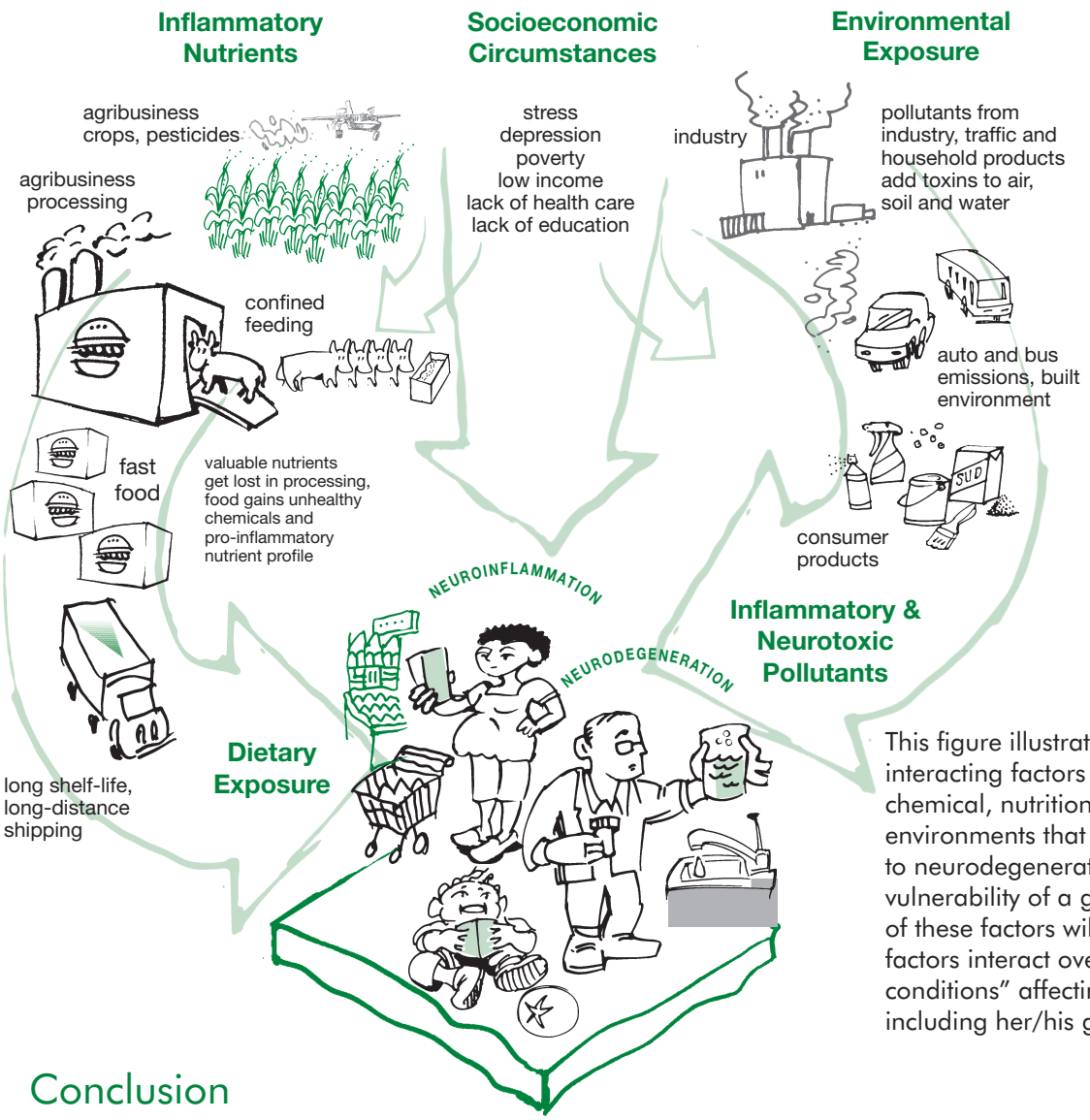
Studies in humans show that although melatonin levels normally decline with age, the levels are more sharply reduced in people with Alzheimer's disease, even in the earliest stages.[368] [369] One therapeutic trial in people with Alzheimer's disease concluded that melatonin supplements can stabilize cognitive decline.[370] Another study in people with Alzheimer's disease in group homes showed that, although melatonin improved sleep patterns, its effects on cognitive function were beneficial only when combined with bright lights during the day.[371] Melatonin supplementation also improved memory and learning in rat models of Alzheimer's disease.[372] Taken together, the evidence is suggestive that ELF-MF could potentially increase risk for Alzheimer's disease by reducing brain levels of neuroprotective melatonin. Human studies have not yet been designed to study this hypothesis.

Other mechanisms proposed to explain potential ELF-MF effects on the brain and biological systems in general include oxidative stress, calcium ion release in immune cells and neurons, apoptosis and necrosis in brain cells, and effects on biomagnetic particles in the brain.[373]

[bf] *The 1.6-fold increased risk was derived from cohort studies. The twofold increased risk was derived from case-control studies.*

[bg] *All included studies used standardized criteria for Alzheimer's diagnosis, and most studies used quantitative estimates of EMF exposure.*

[bh] *Criteria for this study required expert diagnoses and restrictive classification of magnetic field exposure.*



This figure illustrates some of the interacting factors in the modern chemical, nutritional, social and built environments that may be contributing to neurodegenerative disease. The vulnerability of a given individual to any of these factors will depend on how these factors interact over time in the "sea of conditions" affecting the individual – including her/his genetic make-up.

Conclusion

We have reviewed a number of environmental factors that substantially influence the risks of Alzheimer's/dementia and cognitive decline. These include elements of the chemical, nutritional, and social environment, as well as exercise and disease states—which are themselves responsive to many of these same influences. We turn now to examine the role of environmental influences in Parkinson's disease. Subsequently, we will discuss opportunities in policy innovations (in chapter 9) and personal actions to address these influences and reduce the risks for neurodegenerative disease and related Western disease cluster illnesses.

Endnotes

1 Bennett DA, Schneider JA, Arvanitakis Z, et al. Neuropathology of older persons without cognitive impairment from two community-based studies. Neurology. 2006 Jun 27;66(12):1837-44.

2 Qiu C, De Ronchi D, Fratiglioni L. The epidemiology of the dementias: an update. Curr Opin Psychiatry. 2007;20:380-385.

3 Blass DM, Rabins PV. In the Clinic: Dementia. Annals of Internal Medicine. 2008;ITC4:1-16.

4 Wolfe M. Shutting down Alzheimer's. Scientific American. 2006;294(5):72-79.

5 Chafekar SM, Baas F, Scheper W. Oligomer-specific Abeta toxicity in cell models is mediated by selective uptake. Biochim Biophys Acta. 2008;1782(9):523-31.

6 Resende R, Ferreiro E, Pereira C, et al. Neurotoxic effect of oligomeric and fibrillar species of amyloid-beta peptide 1-42: Involvement of endoplasmic reticulum calcium release in oligomer-induced cell death. Neuroscience. 2008;155(3):725-37.

7 Wolfe M. Shutting down Alzheimer's. Scientific American. 2006;294(5):72-79.

8 Zigman W, Lott I. Alzheimer's disease in Down syndrome: neurobiology and risk. Ment Retard Dev Disabil Res Rev. 2007;13(3):2287-2293.

9 Leverenz J, Raskind M. Early amyloid deposition in the medial temporal lobe of young Down syndrome patients: a regional quantitative analysis. Exp Neurol. 1998;150:296–304.

10 Lott I, Head E, Doran E, et al. Beta-amyloid, oxidative stress, and down syndrome. Curr Alzheimer Res. 2006;3(5):521-528.

11 Nunomura A, Perry G, Pappolla M, et al. Neuronal oxidative stress precedes amyloid-beta deposition in Down syndrome. J Neuropathol Exp Neurol. 2000;59:1011–1017.

12 Tansley G, Burgess B, Bryan M, et al. The cholesterol transporter ABCG1 modulates the subcellular distribution and proteolytic processing of beta-amyloid precursor protein. J Lipid Res. 2007;48(5):1022-1034.

13 Lott I, Head E, Doran Busciglio J. Beta-amyloid, oxidative stress, and down syndrome. Curr Alzheimer 2006;3(5):521-528.

14 Nunomura A, Perry G, Pappolla M, et al. Neuronal oxidative stress precedes amyloid-beta deposition in Down syndrome. J Neuropathol Exp Neurol 2000;59:1011–1017.

15 Munoz DG, Feldman H. Causes of Alzheimer's disease. CMAJ. 2000;162(1):65-72.

16 Farrer LA, Cupples LA, Haines JL, et al. Effects of age, sex, and ethnicity on the association between apolipoprotein E genotype and Alzheimer disease. A meta-analysis. APOE and Alzheimer Disease Meta Analysis Consortium. JAMA. 1997 Oct 22-29;278(16):1349-56.

17 Raber J, Huang Y, Ashford JW. ApoE genotype accounts for the vast majority of AD risk and pathology. Neurobiol Aging. 2004 May-Jun;25(5):641-50.

18 Haan MN, Shemanski L, Jagust WJ, et al. The role of APOE epsilon4 in modulating effects of other risk factors for cognitive decline in elderly persons. JAMA. 1999 Jul 7;282(1):40-6.

19 Farrer LA, Cupples LA, Haines JL, et al. Effects of age, sex, and ethnicity on the association between apolipoprotein E genotype and Alzheimer disease. A meta-analysis. APOE and Disease Meta Analysis Consortium. JAMA. 1997 Oct 22-29;278(16):1349-56.

20 Corbo RM, Scacchi R. Apolipoprotein E allele distribution in the world. Is APOE4 a "thrifty" allele? Ann. Hum. Genet. 1999;63:301-310.

21 Farrer LA, Cupples LA, Haines JL, et al. Effects of age, sex, and ethnicity on the association between apolipoprotein E genotype and Alzheimer disease. A meta-analysis. APOE and Alzheimer Disease Meta Analysis Consortium. JAMA. 1997 Oct 22-29;278(16):1349-56.

22 Tyas SL, Salazar JC, Snowdon DA, et al. Transitions to mild cognitive impairments, dementia, and death: findings from the Nun Study. Am J Epidemiol. 2007 Jun 1;165(11):1231-8.

23 Sawyer K, Sachs-Ericsson N, Preacher KJ, et al. Racial Differences in the Influence of the APOE Epsilon 4 Allele on Cognitive Decline in a Sample of Community-Dwelling Older Adults. Gerontology. 2008 Jun 5. [Epub ahead of print]

24 Ordovas JM, Mooser V. The APOE locus and the pharmacogenetics of lipid response. Curr Opin Lipidol. 2002 Apr;13(2):113-7.

25 Song Y, Stampfer MJ, Liu S. Meta-analysis: apolipoprotein E genotypes and risk for coronary heart disease. Ann Intern Med. 2004 Jul 20;141(2):137-47.

26 Martins IJ, Hone E, Foster JK, et al. Apolipoprotein E, cholesterol metabolism, diabetes, and the convergence of risk factors for Alzheimer's disease and cardiovascular disease. Mol Psychiatry. 2006 Aug;11(8):721-36.

27 Corbo RM, Scacchi R. Apolipoprotein E (APOE) allele distribution in the world. Is APOE*4 a 'thrifty' allele? Ann Hum Genet. 1999 Jul;63(Pt 4):301-10.

28 Wilson PW, Schaefer EJ, Larson MG, et al. Apolipoprotein E alleles and risk of coronary disease. A meta-analysis. Arterioscler Thromb Vasc Biol. 1996 Oct;16(10):1250-5.

29 Lane RM, Farlow MR. Lipid homeostasis and apolipoprotein E in the development and progression of Alzheimer's disease. J Lipid Res. 2005 May;46(5):949-68.

30 Dosunmu R, Wu J, Basha MR, et al. Environmental and dietary risk factors in Alzheimer's disease. Expert Rev. Neurotherapeutics. 2007;7(7):887-900.

31 Kivipelto M, Rovio S, Ngandu T, et al. Apolipoprotein E epsilon4 magnifies lifestyle risks for dementia: a population based study. J Cell Mol Med. 2008 Mar 4. [Epub ahead of print]

32 Hendrie HC, Ogunniyi A, Hall KS, et al. Incidence of dementia and Alzheimer disease in 2 communities: Yoruba residing in Ibadan, Nigeria, and African Americans residing in Indianapolis, Indiana. JAMA. 2001 Feb 14;285(6):739-47.

33 Gureje O, Ogunniyi A, Baiyewu O, et al. APOE epsilon4 is not associated with Alzheimer's disease in elderly Nigerians. Ann Neurol. 2006 Jan;59(1):182-5.

34 Murrell JR, Price B, Lane KA, et al. Association of apolipoprotein E genotype and Alzheimer disease in African Americans. Arch Neurol. 2006 Mar;63(3):431-4.

35 Ogunniyi A, Baiyewu O, Gureje O, et al. Epidemiology of dementia in Nigeria: results from the Indianapolis-Ibadan study. Eur J Neurol. 2000 Sep;7(5):485-90.

36 Osuntokun BO, Sahota A, Ogunniyi AO, et al. Lack of an association between apolipoprotein E epsilon 4 and Alzheimer's disease in elderly Nigerians. Ann Neurol. 1995 Sep;38(3):463-5.

37 Sahota A, Yang M, Gao S, et al. Apolipoprotein E-associated risk for disease in the African-American population is genotype dependent. Neurol. 1997 Oct;42(4):659-61.

38 Yang Y, Ruiz-Narvaez E, Kraft P, et al. Effect of apolipoprotein genotype and saturated fat intake on plasma lipids and myocardial infarction in the Central Valley of Costa Rica. Hum Biol. 2007 Dec;79(6):637-47.

39 Haan MN, Shemanski L, Jagust WJ, et al. The role of APOE epsilon4 in modulating effects of other risk factors for cognitive decline in elderly persons. JAMA. 1999 Jul 7;282(1):40-6.

40 Blair CK, Folsom AR, Knopman DS, et al. Atherosclerosis Risk in Communities (ARIC) Study Investigators. APOE genotype and cognitive decline in a middle-aged cohort. Neurology. 2005 Jan 25;64(2):268-76.

41 Stewart W, Schwartz B, Simon D, et al. ApoE genotype, past adult lead exposure, and neurobehavioral function. Environ Health Perspect. 2002;110(5):501-505.

42 Schmechel DE, Browndyke J, Ghio A. Strategies for dissecting genetic-environmental interactions in neurodegenerative disorders. Neurotoxicology. 2006;27(5):637-657.

43 Shih RA, Hu H, Weisskopf MG, et al. Cumulative lead dose and cognitive function in adults: a review of studies that measured both blood lead and bone lead. Environ Health Perspect. 2007 Mar;115(3):483-92.

44 Weisskopf MG, Wright RO, Schwartz J, et al. Cumulative lead exposure and prospective change in cognition among elderly men. Am J Epidemiology. 2004;160(12):1184-93.

45 Shih RA, Glass TA, Bandeen-Roche K, et al. Environmental lead exposure and cognitive function in community-dwelling older adults. Neurology 2006;67:1556-62.

46 Weisskopf MG, Proctor SP, Wright RO, et al. Cumulative lead exposure and cognitive performance among elderly men. Epidemiology. 2007;18:59-66.

47 Stewart W, Schwartz B, Simon D, et al. ApoE Genotype, Past Adult Lead Exposure, and Neurobehavioral Function. Environ Health Perspect. 2002;110(5).

48 Weisskopf MG, Wright RO, Schwartz J, et al. Cumulative lead exposure and cognitive performance among elderly men. Epidemiology 2007;18:59-66.

49 Basha MR, Murali M, Siddiqi HK, et al. Lead exposure and its effect on APP proteolysis and AB aggregation. FASEB J. 2005;19:2083-4.

50 Weisskopf MG, Proctor SP, Wright RO, et al. Cumulative lead exposure and cognitive performance among elderly men. Epidemiology 2007;18:59-66.

51 Stewart W, Schwartz B, Simon D, et al. ApoE Genotype, Past Adult Lead Exposure, and Neurobehavioral Function. Environ Health Perspect. 2002;110(5).

52 Ibid.

53 Wu J, Basha MR, Brock B, et al. Alzheimer's disease (AD)-like pathology in aged monkeys after infantile exposure to environmental metal lead (Pb): evidence for a developmental origin and environmental link for AD. J Neurosci. 2008;28(1):3-9.

54 Basha MR, Wei W, Bakheet SA, et al. The fetal basis of amyloidogenesis: exposure to lead and latent overexpression of amyloid precursor protein and beta-amyloid in the aging brain. J Neurosci. 2005;25(4):823-829.

55 Lahiri DK, Maloney B, Basha MR et al. How and when environmental agents and dietary factors affect the course of Alzheimer's disease: the LEARn model (latent early-life associated regulation) may explain the triggering of AD. Current Alzheimer Research. 2007;4:219-228.

56 Walton JR. Human range dietary aluminum equivalents cause cognitive deterioration in aged rats. Presented at the 24th International Neurotoxicology Conference. November, 2007. San Antonio, Texas.

57 Walton JR. A longitudinal study of rats chronically exposed to aluminum at human dietary levels. Neurosci Lett. 2007;412:29-33.

58 Walton JR. Human range dietary aluminum equivalents cause cognitive deterioration in aged rats. Presented at the 24th International Neurotoxicology Conference. November, 2007. San Antonio, Texas. Currently in preparation for publication.

59 Greger JL. Aluminum metabolism. Annu. Rev. Nutr. 1993;12:43-63.

60 Walton JR. longitudinal study of rats chronically exposed to aluminum at human dietary levels. Neurosci Lett. 2007;412:29-33.

61 Saiyed SM, Yokel RA. Aluminium content of some foods and food products in the USA, with aluminium food additives. Food Addit Contam. 2005 Mar;22(3):234-44.

62 Walton JR. Human range dietary aluminum equivalents cause cognitive deterioration in aged rats. Presented at the 24th International Neurotoxicology Conference. November, 2007. San Antonio, Texas. Currently in preparation for publication.

63 Walton JR. An aluminum-based rat model for Alzheimer's disease exhibits oxidative damage, inhibition of PP2A activity, hyperphosphorylated tau, and granulovacuolar degeneration. J Inorg Biochem 2007;101(9):1275-84.

64 Iqbal K, Grundke-Iqbal I. Alzheimer neurofibrillary degeneration: significance, etiopathogenesis, therapeutics and prevention. J Cell Mol Med. 2008 Jan-Feb;12(1):38-55.

65 Lukiw WJ, Percy ME, Kruck TP. Nanomolar aluminum induces pro-inflammatory and pro-apoptotic gene expression in human brain cells in primary culture. J Inorg Biochem. 2005;99(9):1895-1898.

66 European Food Safety Authority. Safety of aluminium from dietary intake. EFSA Journal. 2008;754:2-4.

67 Greger JL. Aluminum metabolism. Annu Rev Nutr. 1993;13:43-63.

68 Berthon, Guy. Aluminium speciation in relation to aluminum bioavailability, metabolism and toxicity. Coord Chem Rev. 2002;228:319-341.

69 Scientific opinion of the panel of food additives, flavourings, processing aids and food contact materials. The safety of aluminum from dietary intake. EFSA Journal. 2008;754:1-43. p. 29.

70 Byrne J. EFSA sets new intake for aluminium in food. Breaking News on Supplements & Nutrition – Europe July 16,2008. http://www.foodproductiondaily.com/Quality-Safety/EFSA-sets-new-intake-level-for-aluminium-in-food Accessed July 20, 2008.

71 ATSDR. Toxicologic Profile for Aluminum. Draft for Public Comment. Sept. 2006. http://www.atsdr.cdc.gov/toxprofiles/tp22.html Accessed 8/17/08.

72 Pratico D. Alzheimer's disease and oxygen radicals: new insights. Biochem Pharmacol. 2002;63:563-567.

73 Dosunmu R, Wu J, Basha MR, et al. Environmental and dietary risk factors in Alzheimer's disease. Expert Rev. Neurotherapeutics. 2007;7(7):887-900.

74 Silvestri L, Camaschella C. A potential pathogenetic role of iron in Alzeimer's Disease. J Cell Mol Med. 2008 May 1.

75 Lau FC, Shukitt-Hale B, Joseph JA. Nutritional intervention in brain aging: reducing the effects of inflammation and oxidative stress. Subcell Biochem. 2007;42:299-318.

76 Cole GM, Lim GP, Yang F, et al. Prevention of Alzheimer's disease: Omega-3 fatty acid and phenolic anti-oxidant interventions. Neurobiol Aging. 2005;26 Suppl 1:133-136.

77 Brook RD. Air Pollution. What is bad for the arteries might be bad for the veins. Arch Int Med. 2008;168(9):909-911.

78 Ibid.

79 Ibid.

80 Ibid.

81 Baccarelli A, Martinelli I, Zanobetti A, et al. Exposure to particulate air pollution and risk of deep vein thrombosis. Arch Intern Med. 2008 May 12;168(9):920-7.

82 Brook RD. Air Pollution. What is bad for the arteries might be bad for the veins. Arch Int Med. 2008;168(9):909-911.

83 Calderón-Garcidueñas L, Reed W, Maronpot RR, et al. Brain Inflammation and Alzheimer's-like pathology in individuals exposed to severe air pollution. Toxicol Pathol. 2004;32:650-658.

84 Calderón-Garcidueñas L, Solt AC, Henríquez-Roldán C, et al. Long-term air pollution exposure is associated with neuroinflammation, an altered innate immune response, disruption of the blood-brain barrier, ultrafine particulate deposition, and accumulation of amyloid beta-42 and alpha-synuclein in children and young adults.Toxicol Pathol. 2008;36(2):289-310.

85 Calderón-Garcidueñas L, Reed W, Maronpot RR, et al. Brain Inflammation and Alzheimer's-like pathology in individuals exposed to severe air pollution. Toxicol Pathol. 2004;32:650-658.

86 Calderón-Garcidueñas L, Solt AC, Henríquez-Roldán C, et al. Long-term air pollution exposure is associated with neuroinflammation, an altered innate immune response, disruption of the blood-brain barrier, ultrafine particulate deposition, and accumulation of amyloid beta-42 and alpha-synuclein in children and young adults.Toxicol Pathol. 2008;36(2):289-310.

87 Calderón-Garcidueñas L., Franco-Lira M, Torres-Jardon R, et al. Pediatric respiratory and systemic effects of chronic air pollution exposure: nose, lung, heart, and brain pathology. Toxicol Pathol. 2007;35:154-162.

88 Rao DB, Wong BA, McManus BE, et al. Inhaled iron, unlike manganese, is not transported to the rat brain via the olfactory pathway. Toxicol Appl Pharmacol. 2003 Nov 15;193(1):116-26.

89 Tjälve H, Henriksson J. Uptake of metals in the brain via olfactory pathways. Neurotoxicology. 1999 Apr-Jun;20(2-3):181-95.

90 Oberdörster G, Sharp Z, Atudorei V, et al. Translocation of inhaled ultrafine particles to the brain. Inhal Toxicol. 2004 Jun;16(6-7):437-45.

91 Calderón-Garcidueñas L., Franco-Lira M, Torres-Jardon R, et al. Pediatric respiratory and systemic effects of chronic air pollution exposure: nose, lung, heart, and brain pathology. Toxicol Pathol. 2007;35:154-162.

92 Calderón-Garcidueñas L, Reed W, Maronpot RR, et al. Brain Inflammation and Alzheimer's-like pathology in individuals exposed to severe air pollution. Toxicol Pathol. 2004;32:650-658.

93 Calderón-Garcidueñas L, Solt AC, Henríquez-Roldán C, et al. Long-term air pollution exposure is associated with neuroinflammation, an altered innate immune response, disruption of the blood-brain barrier, ultrafine particulate deposition, and accumulation of amyloid beta-42 and alpha-synuclein in children and young adults. Toxicol Pathol. 2008;36(2):289-310.

94 Ibid.

95 Calderón-Garcidueñas L, Mora-Tiscareño A, Ontiveros E, et al. Air pollution, cognitive deficits and brain abnormalities: pilot study with children and dogs. Brain Cogn. 2008 Jun 10. [ahead of print]

96 Campbell A, Oldham M, Becaria A, et al. Particulate matter in polluted air may increase biomarkers of inflammation in mouse brain. Neurotoxicology. 2005;26(1):133-40.

97 Mohankumar SM, Campbell A, Block M, et al. Particulate matter, oxidative stress and neurotoxicity.Neurotoxicology. 2008 May;29(3):478-87.

98 Hartz AM, Bauer B., Block ML, et al. Diesel exhaust particles induce oxidative stress, proinflammatory signaling, and P-glycoprotein up-regulation at the blood-brain barrier. FASEB J. 2008 Aug;22(8):2723-33

99 Mohankumar SM, Campbell A, Block M, et al. Particulate matter, oxidative stress and neurotoxicity. Neurotoxicology. 2008 May;29(3):478-87.

100 Calderón-Garcidueñas L, Reed W, Maronpot RR, et al. Brain Inflammation and Alzheimer's-like pathology in individuals exposed to severe air pollution. Toxicol Pathol. 2004;32:650-658.

101 Hoshino T, Nakaya T, Homan T, et al. Involvement of prostaglandin E2 in production of amyloid-beta peptides both in vitro and in vivo. J Biol Chem. 2007 Nov 9;282(45):32676-88.

102 Kotilinek LA, Westerman MA, Wang Q, et al. Cyclooxygenase-2 inhibition improves amyloid-beta-mediated suppression of memory and synaptic plasticity. Brain. 2008 Mar;131(Pt 3):651-64.

103 Schantz S, Widholm J, Rice D. Effects of PCB exposure on neuropsychological function in children. Environ Health Perspect. 2003 111(3):357-576.

104 Lin K, Guo N, Tsai P, et al. Neurocognitive changes among elderly exposed to PCBs/PCDFs in Taiwan. Environ Health Perspect. 2008;116:184-189.

105 Schantz SL, Gasior DM, Polverejan E, et al. Impairments of memory and learning in older adults exposed to polychlorinated biphenyls via consumption of Great Lakes fish. Environ Health Perspect. 2001;108:605-611.

106 Steenland K, Hein MJ, Cassinelli RT, et al. Polychlorinated biphenyls and neurodegenerative disease mortality in an occupational cohert. Epidemiology. 2006;17(1):8-13.

107 Mele PC, Bowman RE, Levin ED. Behavioral evaluation of perinatal PCB exposure in rhesus monkeys: fixed-interval performance and reinforcement-omission. Neurobehav Toxicol Teratol. 1986;8:131–138.

108 Schantz SL, Levin ED, Bowman Heironimus MP, et al. Effects of perinatal PCB exposure on discrimination-reversal learning in monkeys. Neurotoxicol Teratol. 1989;11:243–250.

109 Seegal RF, Bush B, Brosch KO. Comparison of effects of Aroclors 1016 and 1260 on non-human primate catecholamine function. Toxicology. 1991;66:145–163.

110 Lee DH, Lee IK, Song K. A strong dose-response relation between serum concentrations of persistent organic pollutants and diabetes: results from the National and Examination Survey 1999-2002. Diabetes Care. 2006 Jul;29(7):1638-44.

111 Lee DH, Lee IK, Jin SH, et al. Association between serum concentrations of persistent organic pollutants and insulin resistance among nondiabetic adults: results from the National and Nutrition Examination Survey 1999-2002. Diabetes Care. 2007 Mar;30(3):622-8.

112 Lee DH, Lee IK, Porta M, et al. Relationship between serum concentrations of persistent organic pollutants and the prevalence of metabolic syndrome among non-diabetic adults: results from the National and Nutrition Examination Survey 1999-2002. Diabetologia. 2007 Sep;50(9):1841-51.

113 Ha MH, Lee DH, Jacobs DR. Association between serum concentrations of persistent organic pollutants and self-reported cardiovascular disease prevalence: results from the National Health and Nutrition Survey, 1999-2002. Environ Perspect. 2007 Aug;115(8):1204-9.

114 Arsenescu V, Arsenescu RI, King V, et al. Pcb-77 induces adipocyte differentiation and proinflammatory adipokines and promotes obesity and atherosclerosis. Environ Health Perspect. 2008;116(6):761-768.

115 Song MO, Freedman JH. Activation of mitogen activated protein kinases by PCB126 (3,3',4,4',5-pentachlorobiphenyl) in HepG2 cells. Toxicol Sci. 2005 Apr;84(2):308-18.

116 Ibid.

117 Hennig B, Hammock BD, Slim R, et al. PCB-induced oxidative stress in endothelial cells: modulation by nutrients. Int J Hyg Health. 2002 Mar;205(1-2):95-102.

118 Matsusue K Ishii Y, Ariyoshi N, et al. A highly toxic coplanar polychlorinated biphenyl compound suppresses delta 5 and delta 6 desaturates activities which play key roles in arachidonic acid synthesis in rat liver. Chem. Rev Toxicol. 1999;12:1158-65.

119 Alzoubi KH, Gerges NZ, Aleisa AM, et al. Levothyroxin restores hypothyroidism-induced impairment of hippocampus-dependent learning and memory: Behavioral, electrophysiological, and molecular studies. Hippocampus. 2008 Aug 4. [Epub ahead of print]

120 Hogervorst E, Huppert F, Matthews FE, et al. Thyroid function and cognitive decline in the MRC Cognitive Function and Aging Study. Psychoneuroendocrinology. 2008 Aug;33(7):1013-22.

121 Kamel F, Hoppin JA. Association of pesticide exposure with neurologic dysfunction and disease. Environ Health Perspect. 2004 Jun;112(9):950-8.

122 Kamel F, Engel LS, Gladen BC, et al. Neurologic symptoms in licensed pesticide applicators in the Agricultural Health Study. Hum Exp Toxicol. 2007 Mar;26(3):243-50.

123 Baldi I, Filleul L, Mohammed-Brahim B, et al. Neuropsychologic effects of long-term exposure to pesticides: results from the French phytoner study. Environ Health Perspect. 2001;109:839-844.

124 Kamel F, Hoppin JA. Association of pesticide exposure with neurologic dysfunction and disease. Environ Health Perspect. 2004 Jun;112(9):950-8.

125 Baldi I Filleul L, Mohammed-Brahim B, et al. Neuropsychologic effects of long-term exposure to pesticides: results from the French phytoner study. Environ Health Perspect. 2001;109:839-844.

126 Rosenstock L, Keifer M, Daniell WE, et al Chronic central nervous system effects of acute organophosphate pesticide intoxication. The Pesticide Effects Study Group. Lancet. 1991 Jul 27;338(8761):223-7.

127 Steenland K, Dick RB, Howell RJ, et al. Neurologic function among termiticide applicators exposed to chlorpyrifos. Environ Health Perspect. 2000 Apr;108(4):293-300.

128 Savage EP, Keefe TJ, Mounce LM, et al. Chronic neurological sequelae of acute organophosphate pesticide poisoning. Arch Environ Health. 1988 Jan-Feb;43(1):38-45.

129 Kamel F, Hoppin JA. Association of pesticide exposure with neurologic dysfunction and disease. 2004 Jun;112(9):950-8.

130 Daniell W, Barnhart S, Demers P, et al. Neuropsychological performance among agricultural pesticide applicators. Environ Res. 1992 Oct;59(1):217-28.

131 Ames RG, Steenland K, Jenkins B, et al. Chronic neurologic sequelae to cholinesterase inhibition among agricultural pesticide applicators. Arch Environ Health. 1995 Nov-Dec;50(6):440-4.

132 Kamel F, Hoppin JA. Association of pesticide exposure with neurologic dysfunction and disease. Environ Health Perspect. 2004 Jun;112(9):950-8.

133 Baldi I et al. Neuropsychologic effects of long-term exposure to pesticides: results from the French phytoner study. Environ Health Perspect. 2001;109:839-844.

134 Cole DC et al. Neurobehavioral outcomes among farm and nonfarm rural Ecuadorians. Neurotoxicology and Teratology. 1997;19:277-286.

135 Baldi I, Filleul L, Mohammed-Brahim B, et al. Neuropsychologic effects of long-term exposure to pesticides: results from the French phytoner study. Environ Health Perspect. 2001;109:839-844.

136 The Canadian Study of and Aging: risk factors for Alzheimer's disease in Canada. Neurology. 1994 Nov;44(11):2073-80.

137 Baldi I, Lebailly P, Mohammed-Brahim B, et al. Neurodegenerative diseases and exposure to pesticides in the elderly. Am Journal of Epidemiology 2003;157(5):409-414.

138 Tyas SL, Manfreda J, Strain LA, et al. Risk factors for Alzheimer's disease: a population-based, longitudinal study in Manitoba, Canada. Int J Epidemiol. 2001;30(3):590-7.

139 Gun RT, Korten AE, Jorm AF, et al. Occupational risk factors for Alzheimer disease: a case-control study. Alzheimer Dis Assoc Disord. 1997 Mar;11(1):21-7.

140 Lindsay J, Laurin D, Verreault R, et al. Risk factors for Alzheimer's disease: a prospective analysis from the Canadian Study of Health and Aging. Am J Epidemiol. 2002 Sep 1;156(5):445-53.

141 Bosma H, van Boxtel M, Ponds R, et al. Pesticide exposure and risk of mild cognitive dysfunction. Lancet. 2000;356:912-3.

142 Gauthier E, Fortier I, Courchesne F, et al. Environmental pesticide exposure as a risk factor for Alzheimer's disease: a case-control study. Environ Res. 2001;86:37-45.

143 Kivipelto M, Ngandu T, Fratiglioni L, et al. Obesity and vascular risk factors at midlife and the risk of dementia and Alzheimer disease. Arch Neurol. 2005;62:1556-1560.

144 Biessels GJ, Staekenborg S, Brunner E, et al. Risk of dementia in diabetes mellitus: a systematic review. Lancet Neurol. 2006 Jan;5(1):64-74.

145 Shadlen MF, Larson EB. Risk factors for dementia. UpToDate online medical reference text. Uptodate.com Referenced 6/27/08.

146 Yaffe K, Blackwell T, Kanaya AM, et al. Diabetes, impaired fasting glucose, and development of cognitive impairment in older women. Neurology. 2004;63:658-663.

147 van Oijen M, Okereke OI, Kang JH, et al. Fasting insulin levels and cognitive decline in older women without diabetes. Neuroepidemiology. 2008;30:174-9.

148 Okereke OI, Pollack MN, Hu FB, et al. Plasma C-peptide levels and rates of cognitive decline in older, community-dwelling women without diabetes. Psychoneuroendocrinology. 2008;33(4)455-61, 2008.

149 Irie F, Fitzpatrick A, Lopez O, et al. Enhanced risk for Alzheimer disease in persons with type 2 diabetes and apoE4. Arch Neurol. 2008;65:89-93.

150 Lovestone S. Diabetes and dementia: is the brain another site of end-organ damage? Neurology. 1999;53:1907.

151 Irie F, Fitzpatrick A, Lopez O, et al. Enhanced risk for disease in persons with type 2 diabetes and apoE4. Arch Neurol. 2008;65:89-93.

152 Peila R, Rodriguez B, Launer L. Type 2 diabetes, apoE gene, and the risk for dementia and related pathologies: the Honolulu-Asia aging study. Diabetes. 2002;51:1256-1262.

153 Gustafson D. Adiposity indices and dementia. Lancet Neurol. 2006 Aug;5(8):713-20.

154 Kivipelto M, Ngandu T, Fratiglioni L, et al. Obesity and vascular risk factors at midlife and the risk of dementia and disease. Arch Neurol. 2005;62:1556-1560.

155 Gustafson DR, Rothenberg E, Blennow K, et al. An 18-year follow up of overweight and risk for Alzheimer's disease. Arch Intern Med. 2003;163:1524–28.

156 Rosengren A, Skoog I, Gustafson D, et al. Body mass index, other cardiovascular risk factors, and hospitalization for dementia. Arch Intern Med. 2005;165:321–26.

157 Luchsinger JA, Patel B, Tang MX, et al. Measures of adiposity and dementia risk in elderly persons. Arch Neurol. 2007 Mar;64(3):392-8.

158 Whitmer RA, Gunderson EP, Barrett-Connor E, et al. Obesity in middle age and future risk of dementia: a 27 year longitudinal population based study. BMJ. 2005 Jun 11;330(7504):1360.

159 Nourhashemi F, Deschamps V, Larrieu S, et al. Body mass index and incidence of dementia: the PAQUID study. Neurology. 2003; 60:117–19.

160 Stewart R, Masaki K, Xue QL, et al. A 32-year prospective study of change in body weight and incident dementia: the Honolulu-Asia Aging Study. Arch Neurol. 2005; 62:55–60.

161 Whitmer RA, Gunderson EP, Barrett-Connor E, et al. Obesity in middle age and future risk of dementia: a 27 year longitudinal population based study. BMJ. 2005 Jun 11;330(7504):1360.

162 Elias MF, Elias PK, Sullivan LM, et al. Obesity, diabetes and cognitive deficit: the Framingham Heart Study. Neurobiol Aging. 2005; 26 Suppl 1:11-6.

163 Waldstein SR, Katzel LI. Interactive relations of central versus total obesity and blood pressure to cognitive function. Int J Obes (Lond) 2006; 30: 201–17.

164 Cournot M, Marquié JC, Ansiau D, et al. Relation between body mass index and cognitive function in healthy middle-aged men and women. Neurology. 2006 Oct 10;67(7):1208-14.

165 Waldstein SR, Katzel LI. Interactive relations of central versus total obesity and blood pressure to cognitive function. Int J Obes (Lond). 2006;30:201–17.

166 Jagust W, Harvey D, Mungas D, et al. Central obesity and the aging brain. Arch Neurol. 2005 Oct;62(10):1545-8.

167 Ward MA, Carlsson CM, Trivedi MA, et al. The effect of body mass index on global brain volume in middle-aged adults: a cross sectional study. BMC Neurol. 2005 Dec 2;5:23.

168 Jagust W, Harvey D, Mungas D, et al. Central obesity and the aging brain. Arch Neurol. 2005 Oct;62(10):1545-8.

169 Brickman AM, Schupf N, Manly JJ, et al. Brain morphology in older African Americans, Caribbean Hispanics, and Whites from northern Manhattan. Neurol. 2008 Aug;65(8):1053-61.

170 Gustafson D, Lissner L, Bengtsson C, et al. A 24-year follow-up of body mass index and cerebral atrophy. Neurology. 2004 Nov 23;63(10):1876-81. Summary for patients in: Neurology. 2004 Nov 23;63(10):E19-20.

171 Gazdzinski S, Kornak J, Weiner MW, et al. Body mass index and magnetic resonance markers of brain integrity in adults. Ann Neurol. 2008 May;63(5):652-7.

172 Razay, G, Vreugdenhil, A, Wilcock, G. The metabolic syndrome and Alzheimer disease. Arch Intern Med. 2007;64:93-6.

173 Kalmijn S, Foley D, White L, et al. Metabolic cardiovascular syndrome and risk of dementia in Japanese-American elderly men. The Honolulu-Asia aging study. Arterioscler Thromb Vasc Biol. 2000;20:2255-60.

174 Yaffe K, Kanaya A, Lindquist K, et al. The metabolic syndrome, inflammation, and risk of cognitive decline. JAMA. 2004; 292:2237-42.

175 Yaffe K, Haan M, Blackwell T, et al. Metabolic syndrome and cognitive decline in elderly Latinos: findings from the Sacramento Area Latino Study of Aging study. J Am Geriatr Soc. 2007 May;55(5):758-62.

176 Muller M, Tang MX, Schupf N, et al. Metabolic syndrome and dementia risk in a multiethnic elderly cohort. Dement Geriatr Cogn Disord. 2007;24:185-92.

177 Yaffe K, Kanaya A, Lindquist K, et al. The metabolic syndrome, inflammation, and risk of cognitive decline. JAMA. 2004; 292:2237.

178 Rafnsson SB, Deary IJ, Smith FB, et al. Cognitive decline and markers of inflammation and hemostasis: the Edinburgh artery study. J Am Geriatr Soc. 2007;55:700.

179 Schram MT, Euser SM, de Craen AK, et al. Systemic markers of inflammation and cognitive decline in old age. J Am Geriatr Soc. 2007;55:708-16.

180 Tan ZS, Beiser AS, Vasan RS, et al. Inflammatory markers and the risk of Alzheimer disease: the Framingham Study. Neurology. 2007;68:1902-8.

181 Yaffe K, Kanaya A, Lindquist K, et al. The metabolic syndrome, inflammation, and risk of cognitive decline. JAMA. 2004; 292:2237-42.

182 Yaffe K, Haan M, Blackwell T, et al. Metabolic syndrome and cognitive decline in elderly Latinos: findings from the Sacramento Area Latino Study of Aging study. J Am Geriatr Soc. 2007 May;55(5):758-62.

183 Dik MG, Jonker C, Hack CE, et al. Serum inflammatory proteins and cognitive decline in older persons. Neurology. 2005 26;64(8):1371-7.

184 Engelhart MJ, Geerlings MI, Meijer J, et al. Inflammatory proteins in plasma and the risk of dementia: the Rotterdam study. Arch Neurol. 2004 May;61(5):668-72.

185 Yaffe K, Lindquist K, Penninx BW, et al. Inflammatory markers and cognition in well-functioning African-American and white elders. Neurology. 2003 Jul 8;61(1):76-80.

186 Schmidt R, Schmidt H, Curb JD, et al. Early inflammation and dementia: a 25-year follow-up of the Honolulu-Asia Aging Study. Ann Neurol. 2002 Aug;52(2):168-74.

187 Weaver JD, Huang MH, Albert M, et al. Interleukin-6 and risk of cognitive decline: MacArthur studies of successful aging. Neurology. 2002 Aug 13;59(3):371-8.

188 Weuve J, Ridker PM, Cook NR, et al. High-sensitivity C-reactive protein and cognitive function in older women. Epidemiology. 2006 Mar;17(2):183-9.

189 Holovoet P, Lee DH, Steffes M, et al. Association between circulating oxidized Low-density lipoprotein and incidence of the metabolic syndrome. JAMA. 2008;299:2287-2293.

190 Albert MS. Changing the trajectory of cognitive decline? N Engl J Med. 2007;357(5):502-3.

191 Fischer A, Sananbenesi Fm Wang X, et al. Recovery of learning and memory is associated with chromatin remodeling. Nature. 2007;447:178-82.

192 Van Praag H, et al. Neural consequences of environmental enrichment. Nat Rev Neurosci. 2000;1:191-8.

193 Shadlen MF et al. Risk factors for dementia. UpToDate online medical reference text. Uptodate.com Referenced 6/27/08.

194 Fratiglioni L, Palliard-Borg S, Winblad B. An active and socially integrated lifestyle in late life might protect against dementia. Lancet Neurol. 2004;3(6):343-53.

195 Barnes LL, Mendes de Leon CF, Wilson RS, et al. Social resources and cognitive decline in a population of older African Americans and whites. Neurology. 2004;63(12):2322-6.

196 Rovio S, Kareholt I, Viitanen B, et al. Leisure-time physical activity at midlife and the risk of dementia and Alzheimer's disease. Lancet Neurol. 2005;4(11):705-11.

197 Wilson RS, Scherr PA, Schneider JA, et al. Relation of cognitive activity to risk of developing Alzheimer disease. Neurology. 2007;69(20):1911-20,

198 Flynn MG, McFarlin BK, Phillips MD, et al. Toll-like receptor 4 and CD14 mRNA expression are lower in resistive exercise-trained elderly women. J Appl Physiol. 2003 Nov;95(5):1833-42.

199 Brooks SV, Vasilaki A, Larkin LM, et al. Repeated bouts of aerobic exercise lead to reductions in skeletal muscle free radical generation and nuclear factor kappaB activation. J Physiol. 2008;586(16):3979-90.

200 Attipoe S, Park JY, Fenty N, et al. Oxidative stress levels are reduced in postmenopausal women with exercise training regardless of hormone replacement therapy status. J Women Aging. 2008;20(1-2):31-45.

201 Rozanski A, Blumenthal JA, Kaplan J. Impact of psychological factors on the pathogenesis of cardiovascular disease and implications for therapy. Circulation. 1999 Apr 27;99(16):2192-217.

202 Geerlings MI, Schmand B, Braam AW, et al. Depressive symptoms and risk of Alzheimer's disease in more highly educated older people. J Am Geriatr Soc. 2000 Sep;48(9):1092-7.

203 Ownby RL, Crocco E, Acevedo A, et al. Depression and risk for Alzheimer disease: systematic review, meta-analysis, and metaregression analysis. Arch Gen Psychiatry. 2006;63:530–538.

204 Chen P, Ganguli M, Mulsant BH, et al. The temporal relationship between depressive symptoms and dementia: a community-based prospective study. Arch Gen Psychiatry. 1999;56:261–266.

205 Ganguli M, Du Y, Dodge HH, et al. Depressive symptoms and cognitive decline in late life: a prospective epidemiological study. Arch Gen Psychiatry. 2006;63:153–160.

206 Ownby RL, Crocco E, Acevedo A, et al. Depression and risk for Alzheimer disease: systematic review, meta-analysis, and metaregression analysis. Arch Gen Psychiatry. 2006;63:530–538.

207 Wilson RS, Evans DA, Bienias JL, et al. Proneness to psychological distress is associated with risk of Alzheimer's disease. Neurology. 2003 Dec 9;61(11):1479-85.

208 Wilson RS, Arnold SE, Schneider JA, et al. Chronic psychological distress and risk of Alzheimer's disease in old age. Neuroepidemiology. 2006;27(3):143-53.

209 Videbech P, Ravnkilde B. Hippocampal volume and depression: a meta-analysis of MRI studies. Am J Psychiatry. 2004;161:1957–1966

210 Campbell S, Marriott M, Nahmias C, et al. Lower hippocampal volume in patients suffering from depression: a meta-analysis. Am J Psychiatry. 2004;161:598–607.

211 Geerlings MI, Schmand B, Braam AW, et al. Depressive symptoms and risk of Alzheimer's disease in more highly educated older people. J Am Geriatr Soc. 2000 Sep;48(9):1092-7.

212 Stress System Malfunction Could Lead to Serious, Life Threatening Disease. NIHBackgrounder. http://www.nih.gov/news/pr/sep2002/nichd-09.htm . Accessed 8/08.

213 Johnson JD, O'Connor KA, Deak T, et al. Prior stressor exposure primes the HPA axis. Psychoneuroendocrinology. 2002 Apr;27(3):353-65.

214 Parker KJ, Schatzberg AF, Lyons DM. Neuroendocrine aspects of hypercortisolism in major depression. Horm Behav. 2003;43:60–66.

215 Magri F, Cravello L, Barili L, et al. Stress and dementia: the role of the hypothalamicpituitary-adrenal axis. Aging Clin Exp Res. 2006 18(2):167-70.

216 Sapolsky RM, Uno H, Rebert CS, et al. Hippocampal damage associated with prolonged glucocorticoid exposure in primates. J Neurosci. 1990;10:2897–2902.

217 Lupien SJ, Schwartz G, Ng YK, et al. The Douglas Hospital Longitudinal Study of Normal and Pathological Aging: summary of findings. J Psychiatry Neurosci. 2005 Sep;30(5):328-34.

218 Magri F, Cravello L, Barili L, et al. Stress and dementia: the role of the hypothalamicpituitary-adrenal axis. Aging Clin Exp Res. 2006 Apr;18(2):167-70.

219 Wilson RS, Evans DA, Bienias JL, et al. Proneness to psychological distress is associated with risk of Alzheimer's disease. Neurology. 2003 Dec 9;61(11):1479-85.

220 Kang JE, Cirrito JR, Dong H, et al. Acute stress increases interstitial fluid amyloid-beta via corticotropin-releasing factor and neuronal activity. Proc Natl Acad Sci U S A. 2007 Jun 19;104(25):10673-8.

221 Dong H, Goico B, Martin M, et al. Modulation of hippocampal cell proliferation, memory, and amyloid plaque deposition in APPsw (Tg2576) mutant mice by isolation stress. Neuroscience. 2004;127(3):601-9.

222 Ross R. Atherosclerosis—an inflammatory disease. N Eng J Med. 1999;340:115-126.

223 Rozanski A, Blumenthal JA, Kaplan J. Impact of psychological factors on the pathogenesis of cardiovascular disease and implications for therapy. Circulation. 1999 Apr 27;99(16):2192-217.

224 Suarez EC, Krishnan RR, Lewis JG. The relation of severity of depressive symptoms to monocyte-associated proinflammatory cytokines and chemokines in apparently healthy men. Psychosom Med. 2003 May-Jun;65(3):362-8.

225 Kiecolt-Glaser JK, Preacher KJ, MacCallum RC, et al. Chronic stress and age-related increases in the proinflammatory cytokine IL-6. Proc Natl Acad Sci U S A. 2003 Jul 22;100(15):9090-5.

226 Kiecolt-Glaser JK, Belury MA, Porter K, et al. Depressive symptoms, omega-6:omega-3 fatty acids, and inflammation in older adults. Psychosom Med. 2007 Apr;69(3):217-24.

227 Maes M, Christophe A, Bosmans E, et al. In humans, serum polyunsaturated fatty acid levels predict the response of proinflammatory cytokines to psychologic stress. Biol Psychiatry. 2000 May 15;47(10):910-20.

228 Johnson JD, O'Connor KA, Deak T, et al. Prior stressor exposure sensitizes LPS-induced cytokine production. Brain Behav Immun. 2002 Aug;16(4):461-76.

229 Bierhaus A, Wolf J, Andrassy M, et al. A mechanism converting psychosocial stress into mononuclear cell activation. Proc Natl Acad Sci U S A. 2003 Feb 18;100(4):1920-5.

230 Blumenthal JA, Sherwood A, Babyak MA, et al. Effects of exercise and stress management training on markers of cardiovascular risk in patients with ischemic heart disease: a randomized controlled trial. JAMA. 2005 Apr 6;293(13):1626-34.

231 Tofler GH. Psychosocial factors in coronary and cerebral vascular disease. UpToDate on line medical text. www.uptodate.com. Accessed 7/30/2008.

232 Frasure-Smith N, Lespérance F, Prince RH, et al. Randomised trial of home-based psychosocial nursing intervention for patients recovering from myocardial infarction. Lancet. 1997 Aug 16;350(9076):473-9.

233 Jones DA, West RR. Psychological rehabilitation after myocardial infarction: multicentre randomised controlled trial. BMJ. 1996 Dec 14;313(7071):1517-21.

234 Ngandu T, von Strauss E, Helkala et al. Education and dementia: what lies behind the association? Neurology 2007;69(14):1442-1450.

235 Fratiglioni L, Winblad B, von Strauss E. Prevention of disease and dementia. Major findings from the Kungsholmen Project. Physiol Behav. 2007;92(1-2):98-104

236 Fotenos A, Mintun M, Snyder A, et al. Brain volume decline in aging: evidence for a relation between socioeconomic status, preclinical Alzheimer disease, and reserve. Arch Neurol. 2008;65(1):113-120.

237 Stampfer MJ, Hu FB, Manson JE, et al. Primary prevention of coronary heart disease in women through diet and lifestyle. N Engl J Med. 2000 Jul 6;343(1):16-22.

238 De Logeril M, Salen P, Martin JL, et al. Mediterranean diet, traditional risk factors, and the rate of cardiovascular complications after myocardial infarction: final report of the Lyon diet heart study. Circulation 1999;99:797-785.

239 Parrott MD, Greenwood CE. Dietary influences on cognitive function with aging. Ann NY Acad Sci. 2007;114:389-397.

240 Dosunmu R, Wu J, Basha MR, et al. Environmental and dietary risk factors in Alzheimer's disease. Expert Rev. Neurotherapeutics. 2007;7(7):887-900.

241 Morris, MC. Diet and Disease: what the evidence shows. MedGenMed, 6(1): 1-5, 2004.

242 Ibid.

243 Barberger-Gateau P, Raffaitin C, Letenneur L, et al. Dietary patterns and risk of dementia: the Three-City cohort study. Neurology. 2007 Nov 13;69(20):1921-30.

244 Engelhart MJ, Geerlings MI, Ruitenberg A, et al. Diet and risk of dementia: Does fat matter?: The Rotterdam Study. Neurology. 2002 Dec 24;59(12):1915-21.

245 Laurin D, Verreault R, Lindsay J, et al. Omega-3 fatty acids and risk of cognitive impairment and dementia. J Alzheimers Dis. 2003 Aug;5(4):315-22.

246 Morris MC, Evans DA, Bienias JL, et al. Dietary fats and the risk of incident Alzheimer disease. Arch Neurol. 2003 Feb;60(2):194-200. Erratum in: Neurol. 2003 Aug;60(8):1072.

247 Luchsinger JA, Tang MX, Shea S, et al. Caloric intake and the risk of Alzheimer disease. Arch Neurol. 2002 Aug;59(8):1258-63.

248 Kalmijn S, Launer LJ, Ott A, et al. Dietary fat intake and the risk of incident dementia in the Rotterdam Study. Ann Neurol. 1997 Nov;42(5):776-82.

249 Engelhart MJ, Geerlings MI, Ruitenberg et al. Diet and risk of dementia: Does fat matter?: The Rotterdam Study. Neurology. 2002 Dec 24;59(12):1915-21.

250 Beydoun MA, Kaufman JS, Satia JA, et al. Plasma n-3 fatty acids and the risk of cognitive decline in older adults: the Atherosclerosis Risk in Communities Study. Am J Clin Nutr. 2007 85(4):1103-11.

251 Kalmijn S, van Boxtel MP, Ocké M, et al. Dietary intake of fatty acids and fish in relation to cognitive performance at middle age. Neurology. 2004 Jan 27;62(2):275-80.

252 Heude B, Ducimetière P, Berr C; EVAStudy. Cognitive decline and fatty acid composition of erythrocyte membranes--The Study. J Clin Nutr. 2003 Apr;77(4):803-8.

253 Tully AM, Roche HM, Doyle R, et al. Low serum cholesteryl ester-docosahexaenoic acid levels in disease: a case-control study. Br J Nutr. 2003 89(4):483-9.

254 Laitinen MH, Ngandu T, Rovio S, et al. Fat intake at midlife and risk of dementia and disease: a population-based study. Dement Geriatr Cogn Disord. 2006;22(1):99-107.

255 Morris MC, Evans DA, Bienias JL, et al. Dietary fat intake and 6-year cognitive change in an older biracial community population. Neurology. 2004 May 11;62(9):1573-9.

256 Morris MC. Diet and Alzheimer's disease: what the evidence shows. MedGenMed. 2004 Jan 15;6(1):48.

257 Greenwood CE, Winocur G. Cognitive impairment in rats fed high-fat diets: a specific effect of saturated fatty-acid intake. Behav Neurosci. 1996 Jun;110(3):451-9.

258 Gillman M. Dietary Fat. In UpToDate online medical textbook. Accessed 6/30/08.

259 Mensink RP, Katan MB. Effect of dietary fatty acids on serum lipids and lipoproteins. meta-analysis of 27 trials. Arterioscler Thromb. 1992 Aug;12(8):911-9.

260 Mensink RP, Katan MB. of dietary trans fatty acids on high-density and low-density lipoprotein cholesterol levels in healthy subjects. N Engl J Med. 1990 Aug 16;323(7):439-45.

261 Solomon A, Kåreholt I, Ngandu T, et al. Serum cholesterol changes after midlife and late-life cognition: twenty-one-year follow-up study. Neurology. 2007 Mar 6;68(10):751-6.

262 Whitmer RA, Sidney S, Selby J, et al. Midlife cardiovascular risk factors and risk of dementia in late life. Neurology. 2005 Jan 25;64(2):277-81.

263 Notkola IL, Sulkava R, Pekkanen J,et al. Serum total cholesterol, apolipoprotein Eepsilon 4 allele, and Alzheimer's disease. Neuroepidemiology. 1998;17(1):14-20.

264 Reitz C, Luchsinger J, Tang MX, et al. Impact of plasma lipids and time on memory performance in healthy elderly without dementia. Neurology. 2005 Apr 26;64(8):1378-83

265 Shadlen M, Larson E. Risk factors for dementia. In UpToDate online medical textbook. www.uptodate.com. Accessed 6/27/08.

266 Mielke, MM, Zandi, PP, Sjogren, M, et al. High total cholesterol levels in late life associated with a reduced risk of dementia. Neurology 2005; 64:1689.

267 Solomon A, Kareholt, I, Ngandu, T, et al. Serum cholesterol changes after midlife and late-life cognition: twenty-one-year follow-up study. Neurology 2007; 68:751.

268 Puglielli L, Tanzi RE, Kovacs DM. Alzheimer's disease: the cholesterol connection. Nat Neurosci. 2003 Apr;6(4):345-51.

269 Dosunmu R, Wu J, Basha MR, et al. Environmental and dietary risk factors in Alzheimer's disease. Expert Rev. Neurotherapeutics. 2007;7(7):887-900.

270 Refolo LM, Malester B, LaFrancois J, et al. Hypercholesterolemia accelerates the amyloid pathology in a transgenic mouse model. Neurobiol Dis. 2000 Aug;7(4):321-31. Erratum in: Neurobiol Dis 2000 Dec;7(6 Pt B):690.

271 Morris MC. Diet and Alzheimer's disease: what the evidence shows. MedGenMed. 2004 Jan 15;6(1):48.

272 McGahon BM, Martin DS, Horrobin DF, et al. Age-related changes in synaptic function: analysis of the effect of dietary supplementation with omega-3 fatty acids. Neurobiol Aging. 1999;94(1):305-14.

273 Gamoh S, Hashimoto M, Hossain S, et al. Chronic administration of docosahexaenoic acid improves the performance of radial arm maze task in aged rats. Clin Exp Pharmacol Physiol. 2001 Apr;28(4):266-70.

274 Lim GP, Calon F, Morihara T, et al.. diet enriched with the omega-3 fatty acid docosahexaenoic acid reduces amyloid burden in an aged Alzheimer mouse model. J Neurosci. 2005 Mar 23;25(12):3032-40.

275 van Gelder BM, Tijhuis M, Kalmijn S, et al. Fish consumption, n-3 fatty acids, and subsequent 5-y cognitive decline in elderly men: the Zutphen Elderly Study. Am J Clin Nutr. 2007 Apr;85(4):1142-7.

276 Freund-Levi Y, Basun H, Cederholm T, et al. Omega-3 supplementation in mild to moderate Alzheimer's disease: effects on neuropsychiatric symptoms. Int J Geriatr Psychiatry. 2008 Feb;23(2):161-9

277 Freund-Levi Y, Eriksdotter-Jönhagen M, Cederholm T, et al. Omega-3 fatty acid treatment in 174 patients with mild to moderate Alzheimer disease: OmegAD study: a randomized double-blind trial. Arch Neurol. 2006 Oct;63(10):1402-8

278 Schaefer EJ, Bongard V, Beiser AS, et al. Plasma phosphatidylcholine docosahexaenoic acid content and risk of dementia and Alzheimer disease: the Framingham Heart Study. Arch Neurol. 2006 Nov;63(11):1545-50.

279 Morris MC, Evans DA, Tangney CC, et al. Fish consumption and cognitive decline with age in a large community study. Arch Neurol. 2005 Dec;62(12):1849-53.

280 Kalmijn S, van Boxtel MP, Ocké M, et al. Dietary intake of fatty acids and fish in relation to cognitive performance at middle age. Neurology. 2004 Jan 27;62(2):275-80.

281 Heude B, Ducimetière P, Berr C; EVAStudy. Cognitive decline and fatty acid composition of erythrocyte membranes--The Study. J Clin Nutr. 2003 Apr;77(4):803-8.

282 Morris MC, Evans DA, Bienias JL, et al. Consumption of fish and n-3 fatty acids and risk of incident Alzheimer disease. Arch Neurol. 2003 Jul;60(7):940-6.

283 Tully AM, Roche HM, Doyle R, et al. Low serum cholesteryl ester-docosahexaenoic acid levels in Alzheimer's disease: a case-control study. Br J Nutr. 2003 89(4):483-9.

284 Laurin D, Verreault R, Lindsay J, et al. Omega-3 fatty acids and risk of cognitive impairment and dementia. J Alzheimers Dis. 2003 Aug;5(4):315-22.

285 Engelhart MJ, Geerlings MI, Ruitenberg A, et al. Diet and risk of dementia: Does fat matter?: The Rotterdam Study. Neurology. 2002 Dec 24;59(12):1915-21.

286 Barberger-Gateau P, Letenneur L, Deschamps V, et al. Fish, meat, and risk of dementia: cohort study. BMJ. 2002 Oct 26;325(7370):932-3.

287 Conquer JA, Tierney MC, Zecevic J et al, Fatty acid analysis of blood plasma of patients with disease, other types of dementia, and cognitive impairment. Lipids. 2000 Dec;35(12):1305-12.

288 Kalmijn S, Launer LJ, Ott A,et al. Dietary fat intake and the risk of incident dementia in the Rotterdam Study. Ann Neurol. 1997 Nov;42(5):776-82.

289 Kalmijn S, Feskens EJ, Launer LJ, et al. Polyunsaturated fatty acids, antioxidants, and cognitive function in very old men. Am J Epidemiol. 1997 Jan 1;145(1):33-41.

290 Beydoun MA, Kaufman JS, Satia JA, et al. Plasma n-3 fatty acids and the risk of cognitive decline in older adults: the Atherosclerosis Risk in Communities Study. J Clin Nutr. 2007 Apr;85(4):1103-11.

291 Freund-Levi Y, Eriksdotter-Jönhagen M, Cederholm T, et al. Omega-3 fatty acid treatment in 174 patients with mild to moderate Alzheimer disease: OmegAD study: a randomized double-blind trial. Arch Neurol. 2006 Oct;63(10):1402-8

292 Barberger-Gateau P, Raffaitin C, Letenneur L, et al. Dietary patterns and risk of dementia: the Three-City cohort study. Neurology. 2007 Nov 13;69(20):1921-30.

293 Ikemoto A, Ohishi M, Sato Y, et al. Reversibility of n-3 fatty acid deficiency-induced alterations of learning behavior in the rat: level of n-6 fatty acids as another critical factor. J Lipid Res. 2001 Oct;42(10):1655-63.

294 Barberger-Gateau P, Raffaitin C, Letenneur L, et al. Dietary patterns and risk of dementia: the Three-City cohort study. Neurology. 2007 Nov 13;69(20):1921-30.

295 Dai Q, Borenstein AR, Wu Y, et al. Fruit and vegetable juices and Alzheimer's disease: the Kame Project. J Med. 2006; 119:751.

296 Morris, MC, Evans, DA, Tangney, CC, et al. Associations of vegetable and fruit consumption with age-related cognitive change. Neurology. 2006;67:1370-6.

297 Kang JH, Ascherio A, Grodstein F. Fruit and vegetable consumption and cognitive decline in aging women. Ann Neurol. 2005; 57:713-20.

298 Ortega RM, Requejo AM, Andres, et al. Dietary intake and cognitive function in a group of elderly people. Am J Clin Nutr. 1997;66:803-9.

299 Lee L, Kang SA, Lee HO, et al. Relationships between dietary intake and cognitive function level in Korean elderly people. Public Health. 2001;115:133-8.

300 Press D, Alexander M. Prevention of dementia. In UpToDate. www.uptodate.com, accessed 6/30/08.

301 Morris MC, DA, Tagney CC, et al. Associations of vegetable and fruit consumption with age-related cognitive change. Neurology. 2006; 67:1370-6.

302 Chan A, Shea TB. Supplementation with apple juice attenuates presenilin-1 overexpression during dietary and genetically-induced oxidative stress. J Dis. 2006 Dec;10(4):353-8.

303 Morris MC, Evans DA, Tangney CC, et al. Associations of vegetable and fruit consumption with age-related cognitive change. Neurology. 2006; 67:1370-6.

304 Morris MC. Diet and Alzheimer's disease: what the evidence shows. MedGenMed. 2004 Jan 15;6(1):48.

305 Ibid.

306 Yang F, Lim GP, Begum AN, et al. Curcumin inhibits formation of amyloid-beta oligomers and fibrils, binds plaques, and reduces amyloid in vivo. J Biol Chem. 2005 Feb 18;280(7):5892-901.

307 Joseph JA, Shukitt-Hale B, Denisova NA, et al. Reversals of age-related declines in neuronal signal transduction, cognitive, and motor behavioral deficits with blueberry, spinach, or strawberry dietary supplementation. J Neurosci. 1999 Sep 15;19(18):8114-21.

308 Youdim KA, Shukitt-B, Martin A, et al. Short-term dietary supplementation of blueberry polyphenolics: beneficial effects on aging brain performance and peripheral tissue function. Nutr Neurosci. 2000;3:383-97.

309 Casadesus G, Shukitt-Hale B, Stellwagen HM, et al. Modulation of hippocampal plasticity and cognitive behavior by short-term blueberry supplementation in aged rats. Nutr Neurosci. 2004 Oct-Dec;7(5-6):309-16.

310 Arts IC, Hollman PC. Polyphenols and disease risk in epidemiologic studies. Am J Clin Nutr. 2005 Jan;81(1 Suppl):317S-325S. Review.

311 Ibid.

312 Lau FC, Shukitt-Hale B, Joseph JA. Nutritional intervention in brain aging: reducing the effects of inflammation and oxidative stress. Subcell Biochem. 2007;42:299-318. Review.

313 Letenneur L, Proust-Lima C, Le Gouge A, et al. Flavonoid intake and cognitive decline over a 10-year period. Am J Epidemiol. 2007 Jun 15;165(12):1364-71.

314 Commenges D, Scotet V, Renaud S, et al. Intake of flavonoids and risk of dementia. Eur J Epidemiol. 2000 Apr;16(4):357-63.

315 Arts IC, Hollman PC. Polyphenols and disease risk in epidemiologic studies. Am J Clin Nutr. 2005 Jan;81(1 Suppl):317S-325S.

316 Hertog MG, Sweetnam PM, Fehily AM, et al. Antioxidant flavonols and ischemic heart disease in a Welsh population of men: the Caerphilly Study. Am J Clin Nutr. 1997 May;65(5):1489-94.

317 Rosenson RS, Dang DS. Overview of homocysteine in UpToDate online medical text. www.uptodate.com, accessed 6/30/08.

318 Selhub J. Homocysteine metabolism. Annu Rev Nutr.1999;19:217-46.

319 Dang DS. Overview of homocysteine in UpToDate online medical text. www.uptodate.com, accessed 6/30/08.

320 Shadlen M, Larson E. Risk factors for dementia. In UpToDate online medical textbook. www.uptodate.com. Accessed 6/27/08.

321 Clarke R. Homocysteine, B vitamins, and the risk of dementia. Am J Clin Nutr. 2007;85:329-30.

322 Bonaa KH, Njolstad I, Ueland PM, et al. Homocysteine lowering and cardiovascular events after acute myocardial infarction. N Engl J Med 2006; 354:1578-88.

323 Seshadri S et al. Plasma homocysteine as a risk factor for dementia and alzheimer's disease. N Eng J Med. 2002;346:476-83.

324 Luchsinger JA, Tang MX, Miller J, et al. Relation of higher folate intake to lower risk of Alzheimer disease in the elderly. Arch Neurol. 2007;64:86-92.

325 Kalmijn S, Launer LJ, Lindemans J, et al. Total homocysteine and cognitive decline in a community-based sample of elderly subjects: the Rotterdam Study. Am J Epidemiol. 1999 Aug 1;150(3):283-9.

326 Morris MC, Evans DA, Schneider JA, et al. Dietary folate and vitamins B-12 and B-6 not associated with incident Alzheimer's disease. J Alzheimers Dis. 2006 9(4):435-43.

327 Seshadri S, Wolf PA, Beiser AS, et al. Association of plasma total homocysteine levels with subclinical brain injury: cerebral volumes, white matter hyperintensity, and silent brain infarcts at volumetric magnetic resonance imaging in the Framingham Offspring Study. Arch Neurol. 2008 May;65(5):642-9.

328 Durga J, van Boxtel MP, Schouten EG, et al. Effect of 3-year folic acid supplementation on cognitive function in older adults in the FACIT trial: a randomised, double blind, controlled trial. Lancet. 2007;369:208.

329 Press D, Alexander M. Prevention of dementia. In UpToDate. www.uptodate.com, accessed 6/30/08.

330 McMahon JA, Green TJ, Skeaff CM, et al. A controlled trial of homocysteine lowering and cognitive performance. N Engl J Med. 2006;354:2764-72.

331 Shadlen M, Larson E. Risk factors for dementia. In UpToDate online medical textboot. www.uptodate.com. Accessed 6/27/08.

332 Durga J, van Boxtel MP, Schouten EG, et al. Effect of 3-year folic acid supplementation on cognitive function in older adults in the FACIT trial: a randomised, double blind, controlled trial. Lancet. 2007;369:208-16.

333 Hu FB. The Mediterranean diet and mortality – olive oil and beyond. N Engl J Med 2003. 348;26:2595-6.

334 Ibid.

335 de Lorgeril M, Salen P, Martin JL, et al. Mediterranean diet, traditional risk factors, and the rate of cardiovascular complications after myocardial infarction: final report of the Lyon Diet Heart Study. Circulation. 1999 Feb 16;99(6):779-85.

336 van Dam RM, Rimm EB, Willett WC, et al. Dietary patterns and risk for type 2 diabetes mellitus in U.S. men. Ann Intern Med. 2002 Feb 5;136(3):201-9.

337 Panagiotakos DB, Tzima N, Pitsavos C, et al. The association between adherence to the Mediterranean diet and fasting indices of glucose homoeostasis: the ATTICAStudy. J Am Coll Nutr. 2007 Feb;26(1):32-8.

338 Esposito K, Marfella R, Ciotola M, et al. Effect of a Mediterranean-style diet on endothelial dysfunction and markers of vascular inflammation in the metabolic syndrome: a randomized trial. JAMA. 2004 Sep 22;292(12):1440-6.

339 Giugliano D, K. Mediterranean diet and metabolic diseases. Curr Opin Lipidol. 2008 Feb;19(1):63-8.

340 Estruch R, Martínez-González MA, Corella D, et al. Effects of a Mediterranean-style diet on cardiovascular risk factors: a randomized trial. Ann Intern Med. 2006 Jul 4;145(1):1-11.

341 Panza F, Solfrizzi V, Colacicco AM, et al. Mediterranean diet and cognitive decline. Public Health Nutr. 2004 Oct;7(7):959-63.

342 Scarmeas N, Stern Y, Tang MX, et al. Mediterranean diet and risk for Alzheimer's disease. Annal Neurol. 2006 Jun;59(6):912-21.

343 Scarmeas N, Luchsinger JA, Mayeux R, et al. Mediterranean diet and Alzheimer disease mortality. Neurology. 2007 Sep 11;69(11):1084-93.

344 Tolstrup J, Grønbaek M. Alcohol and atherosclerosis: recent insights. Curr Atheroscler Rep. 2007 Aug;9(2):116-24.

345 Shadlen M, Larson E. Risk factors for dementia. In UpToDate online medical textbook. www.uptodate.com. Accessed 6/27/08.

346 Thomas VS, Rockwood KJ. Alcohol abuse, cognitive impairment and mortality among older people. J Am Geriatr Soc. 2001;49:415-20.

347 Haan MN, Wallace R. Can dementia be prevented? Brain aging in a population-based context. Annu Rev Public Health. 2004,25:1-24.

348 Mukamal KJ, Kuller HL, Fitzpatrick AL, et al. Prospective study of alcohol consumption and risk of dementia in older adults. JAMA. 2003;289:1405-1413.

349 Haan MN, Wallace R. Can dementia be prevented? Brain aging in a population-based context. Annu Rev Public Health. 2004,25:1-24.

350 Evans DA, Bienias JL. Alcohol consumption and cognition. N Eng J Med. 2005;352:3:289-90.

351 Peters R, J, Warner J, Beckett N, et al. Alcohol, dementia and cognitive decline in the elderly: a systematic review. Age Ageing. 2008;37(5):505-12.

352 Stampfer MJ, Kang JH, Chen J, et al. Effects of moderate alcohol consumption on cognitive function in women. N Engl J Med. 2005 Jan 20;352(3):245-53.

353 Dufouil C, Tzourio C, Brayne C, et al. Influence of apolipoprotein Egenotype on the risk of cognitive deterioration in moderate drinkers and smokers. Epidemiology. 2000 May;11(3):280-4.

354 Luchsinger JA, Tang MX, Siddiqui M, et al. Alcohol intake and risk of dementia. J Am Geriatr Soc. 2004 Apr;52(4):540-6.

355 Dufouil C, Tzourio C, Brayne C, et al. Influence of apolipoprotein Egenotype on the risk of cognitive deterioration in moderate drinkers and smokers. Epidemiology. 2000 May;11(3):280-4.

356 Truelsen T, Thudium D, Grønbaek M; Copenhagen City Heart Study. Amount and type of alcohol and risk of dementia: the Copenhagen City Study. Neurology. 2002 Nov 12;59(9):1313-9.

357 Luchsinger JA, Tang MX, Siddiqui M, et al. Alcohol intake and risk of dementia. J Am Geriatr Soc. 2004 52(4):540-6.

358 Stampfer MJ, Kang JH, Chen J, et al. Effects of moderate alcohol consumption on cognitive function in women. N Engl J Med. 2005 Jan 20;352(3):245-53.

359 Mukamal KJ, Kuller HL, Fitzpatrick AL, et al. Prospective study of alcohol consumption and risk of dementia in older adults. JAMA. 2003;289:1405-1413.

360 Guiraud A, de Lorgeril M, Zeghichi S, et al. Interactions of ethanol drinking with n-3 fatty acids in rats: potential consequences for the cardiovascular system. Br J Nutr. 2008 Apr 29:1-8.

361 de Lorgeril M, Salen P, Martin JL, et al. Interactions of wine drinking with omega-3 fatty acids in patients with coronary heart disease: a fish-like effect of moderate wine drinking. Am Heart J. 2008 Jan;155(1):175-81.

362 Ibid.

363 García AM, Sisternas Hoyos SP. Occupational exposure to extremely low frequency electric and magnetic fields and Alzheimer disease: a meta-analysis. Int J Epidemiol. 2008 Apr;37(2):329-40.

364 Davanipour A, Sobel E. Magnetic field Exposure: Melatonin Production; Alzheimer's Disease; Breast Cancer. Prepared for the BioInititative Working Group. July, 2007. http://www.bioinitiative.org/report/docs/section_12.pdf Accessed June 1, 2008.

365 García AM, Sisternas A, Hoyos SP. Occupational exposure to extremely low frequency electric and magnetic fields and Alzheimer disease: a meta-analysis. Int J Epidemiol. 2008 Apr;37(2):329-40.

366 Davanipour A, Sobel E. Magnetic field Exposure: Melatonin Production; Alzheimer's Disease; Breast Cancer. Prepared for the BioInititative Working Group. July, 2007. http://www.bioinitiative.org/report/docs/section_12.pdf

367 Ibid.

368 Wu Y, Feenstra M, Zhou J, et al. Molecular changes underlying reduced pineal melatonin levels in disease: alterations in preclinical and clinical stages. J Clin Endocrinol Metab. 2003;88:5898–5906.

369 Liu Zhou J, van Heerikhuize J, et al. Decreased melatonin levels in postmortem cerebrospinal fluid in relation to aging, Alzheimer's disease, and apolipoprotein E-epsilon4/4 genotype. J Clin Metab. 1999;84:323–327.

370 Brusco L, Marquez M, Cardinali D. Melatonin treatment stabilizes chronobiologic and cognitive symptoms in disease. Neuro Lett. 2000;21:39–42

371 Riemersma-van der Lek R, Swaab D, Twisk J, et al. Effect of bright light and melatonin on cognitive and noncognitive function in elderly residents of group care facilities: a randomized controlled trial. J Amer Med Assoc. 2008;299(22):2642-2655.

372 Davanipour A, Sobel E. Magnetic field Exposure: Melatonin Production; Alzheimer's Disease; Breast Cancer. Prepared for the BioInititative Working Group. July, 2007. http://www.bioinitiative.org/report/docs/section_12.pdf

373 García AM, Sisternas A, Hoyos SP. Occupational exposure to extremely low frequency electric and magnetic fields and disease: a meta-analysis. Int J Epidemiol. 2008 37(2):329-40.

Stories of Life Weave the Fabric of The Intergenerational School

Neuroscientist Peter J. Whitehouse MD PhD helps people weave the stories of their lives through memories, aspirations, and active participation in healthy living.

Whitehouse—a professor at Case Western Reserve University, medical doctor, expert in Alzheimer's disease, bioethicist, educator, author, and innovator—thinks beyond the brain as an isolated organ and into the ecology of the world and the systems that enhance prosperity and wellbeing. He is dedicating his life to ensuring that everyone, including those facing cognitive challenges, has a chance to tell personal tales of triumph and tribulation and live fully through the end of life.

Whitehouse and his wife Cathy, a psychologist, founded The Intergenerational School in 2000. The Cleveland public charter school is an award-winning institution for about 145 students in grades K-8 as well as a nurturing environment for over 30 volunteer adults and seniors.

Intergenerational School student and volunteer elder share life stories. *Photo: Peter J. Whitehouse.*

The goal of the school, located at the Fairhill Center for Aging, is to promote life-long learning keyed to developmental learning stages and "a sense of community, a sense of purpose, a sense of legacy."

A glowing profile in a U.S. Department of Education newsletter noted that in 2006 The Intergenerational School was one of just 21 high-poverty schools statewide in which 75 percent of students passed Ohio's standardized reading test. In 2007, 100 percent of third and fourth grade students passed this test.

Everyone benefits as intergenerational relationships are fostered. Young students at the school support elders by visiting, telling and listening to stories, and developing friendships at local long-term care facilities. Although many adult volunteers have memory or cognitive challenges, they mentor children in reading, arts, and hobbies and serve in such roles as library aides or technology troubleshooters. "The most important thing for the elders is that they have a sense that they are keeping their minds active," said Dr. Whitehouse.

FOOD *for* THOUGHT

The stories of the volunteers are encouraging. Mrs. Atwood, an African-American woman in her late 50s who is beginning to have memory problems (and has two sisters with Alzheimer's in nursing homes), volunteers every two weeks. She begins on Wednesday to "joyfully" plan her Thursdays at The Intergenerational School. The responsibility gives her focus and purpose. Another volunteer, Dr. Miller, holds a PhD in the history of medicine and is a relative of Moses Cleaveland who founded the Ohio city. Her participation with the children at the school helps keeps her disorientation and agitation at bay.

Danny George is Whitehouse's co-author of a recently published book, The Myth of Alzheimer's, which challenges conventional ideas about the diagnosis and treatment of Alzheimer's. George has undertaken a systematic observation of the seniors who donate their time at The Intergenerational School to evaluate how their participation benefits their health.

The success of The Intergenerational School supports the hope that we can foster the sharing of intergenerational wisdom in an increasingly complex world, and thus sustain healthy cognition throughout life. It suggests that it is possible to weave a fabric of common stories of diverse life stages that become the shared narrative of a diverse world.

LifeBook

LifeBook is an innovative program developed by Dr. Whitehouse and described in The Myth of Alzheimer's as a "practice in embracing mortality." By embracing mortality, we also embrace living fully. LifeBook helps people consider issues important at the end of life, and can provide a rich portrait of a person's life. The process suggests that people:

- Tell the story of their life – through pictures, letters and other written materials
- Envision what they want for end of life care
- Reflect on their legacy

This can be a powerful and rewarding experience and enormously helpful to the individual as well as family, friends and caregivers.

For more information, go to the www.tisonline.org and www.themythofalzheimers.com

Chapter 8

Environmental Factors in the Development of Parkinson's Disease

Parkinson's disease is a neurodegenerative disorder first formally described in medical literature by James Parkinson in 1817. It usually begins slowly and becomes progressively more severe. The best known clinical symptom is rhythmic tremor of the limbs, which subsides with intentional movement (sometimes called a "resting tremor"), muscular stiffness, slow movement, and stooped posture. Sleep disorders are common. The earliest stages of Parkinson's disease may begin years or even decades before tremor and stiffness become apparent.[1] Constipation, impaired smell discrimination, and excessive sleepiness are sometimes early manifestations of Parkinson's.[2 3 4] In later stages, depression, psychosis, and dementia may appear, although depression may also be an early sign of the disorder.

The earliest stages of Parkinson's disease may begin years or even decades before tremor and stiffness become apparent.

Parkinson's disease typically begins in a person's 50s or 60s and slowly progresses with age. Early onset of Parkinson's disease before age 30 is rare, but up to 10 percent of cases begin by age 40. Descriptions of people with symptoms consistent with Parkinson's disease appeared in ancient time and periodically thereafter.[5] Lack of patient registries, however, makes it difficult to estimate incidence and trends of the disease even in recent times. The range of reported incidence varies from 4.5 to 21 per 100,000 people annually.

Historically, most attention has focused on degeneration of dopamine-producing cells in a portion of the midbrain called the substantia nigra.[a] When they can no longer produce adequate dopamine, neurons elsewhere in the brain are less well regulated and do not behave normally. Then the familiar clinical symptoms begin. But early Parkinson's disease pathology can involve nerves in the autonomic nervous system in the gastrointestinal tract and heart, even

The crane symbolizes health & protection in Asian cultures

[a] *Several neural pathways in the brain use dopamine as the major neurotransmitter. One of those is the pathway from the substantia nigra to the nearby striatum and is sometimes referred to as the nigrostriatal pathway or region. Degeneration of dopamine-producing cells results in lower levels of dopamine along this pathway. Studies described in this chapter variously refer to the substantia nigra, the striatum, or the nigrostriatum.*

before cells in the brain are affected.[6 7] Parkinson's disease may therefore be a more systemic condition.

In classic Parkinson's disease, affected neurons contain Lewy bodies. A major constituent of these cellular inclusions is a naturally occurring protein called alpha-synuclein (AS) that is misfolded and becomes insoluble.[8] Although the normal functions of AS in the brain are not well understood, it is likely to support synaptic nerve transmission via neurotransmitters. Normally, AS does not accumulate in the brain as it does in Parkinson's disease. Some genetic mutations can cause AS to misfold and become insoluble, but there are almost certain to be environmental factors that play a role in cases where genetic influences are not particularly strong.

The mechanism(s) leading to dopaminergic neuron degeneration, including the role of Lewy bodies, are not well understood. Whereas Lewy bodies may represent an initial attempt to sequester misfolded proteins, they may at some point become a trigger for an inflammatory response, which, in turn, damages dopaminergic neurons.

In addition to Lewy bodies, activated microglia are also present in the brains of people with Parkinson's disease and in various laboratory animal models.[9-11] As discussed in chapter 3, microglia are essential to immune function in the brain. When microglia are activated in response to pathologic stimuli, including infectious agents, chemical toxicants, or trauma, they release a variety of inflammatory substances and growth factors that can be both harmful and beneficial, depending on the nature of the stimulus and the degree and duration of the response. If not self-limited or ultimately reversed, microglial activation can be a source of ongoing, chronic inflammation, generating reactive oxygen species (ROS) and causing persistent oxidative stress. In animal models of Parkinson's disease microglial activation persists long after the initiating stimulus is gone. Imaging studies in people with Parkinson's disease show fairly widespread microglial activation in many areas of the brain, consistent with the now generally accepted conclusion that the pathology of Parkinson's disease is not confined to the substantia nigra.[12]

We now know that classic Parkinson's disease is one of a group of disorders with similar clinical symptoms but variations in areas of the brain affected or microscopic findings. People with symptoms resembling classic Parkinson's disease but with certain different features are sometimes said to suffer from "parkinsonism." Some people with parkinsonism lack Lewy bodies in affected areas

of the brain, but their symptoms may be indistinguishable from classic Parkinson's disease.[13] Some forms of parkinsonism may involve more extensive areas of brain injury than classic Parkinson's disease. In fact, boundaries between classic Parkinson's disease and parkinsonism are evolving concepts around which there is no clear consensus at this time.[14] Multiple pathologic mechanisms are likely to converge to cause a common clinical syndrome. Studies attempting to identify underlying causal factors, therefore, need to grapple with what appears to be considerable heterogeneity in the pathways leading to Parkinson's disease or parkinsonism.

People with symptoms resembling classic Parkinson's disease but with certain different features are sometimes said to suffer from "parkinsonism."

The Causes of Parkinson's Disease

Genetic Contributors

The origins of Parkinson's disease have been debated for decades. In the early 20th century, a small percentage of cases were noted to have affected family members, suggesting a genetic predisposition, but the overwhelming remainder appeared to be sporadic. In the 1990s, a large study of thousands of white male twins enrolled in a World War II veteran database attempted to estimate the extent to which genetic factors play a role in causing Parkinson's disease. The authors concluded that genetic predisposition was a strong determinant of risk in early-onset Parkinson's disease (before age 50) but that genetic factors do not play a major role in causing typical Parkinson's.[15]

More recent studies have identified a number of susceptibility genes that may play a role alone or in various combinations even in later-onset Parkinson's.[16] [17] [b] These candidate genes influence many different biologic processes including levels of neurotransmitters such as dopamine and their receptors, metabolism and excretion of potentially toxic compounds, and protein aggregation. Most investigators conclude that a number of susceptibility genes help to create the conditions in which environmental factors further influence events leading to clinical Parkinson's disease. Strong genetic influences are more important in early-onset Parkinson's than in more typical Parkinson's disease, where perhaps more numerous but weaker susceptibility genes play a less prominent role.

[b] *Several genes are associated with increases in Parkinson's disease risk, including parkin, alpha-synuclein, DJ-1, PINK-1, MAO-B, LRRK2, and UCHL-1, but they account for only a small number of Parkinson's disease cases.*

Environmental Contributors

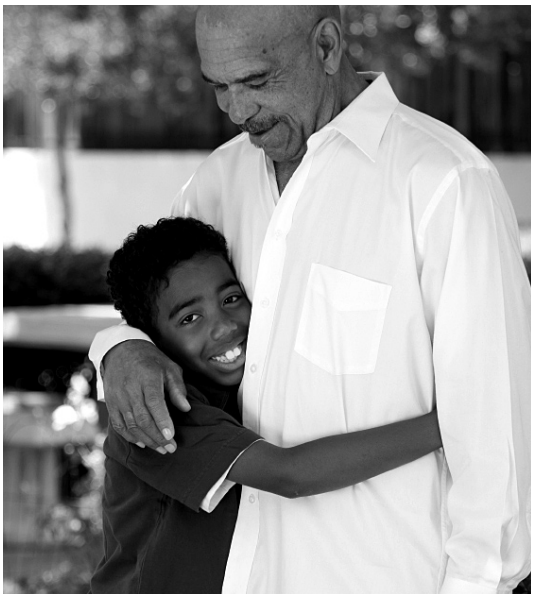
In the 1980s case reports of several individuals who acutely developed Parkinson-like symptoms after injecting a "new synthetic heroin" sparked interest in finding environmental agents that might cause the disorder.[18] MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) contaminated a batch of illicit meperidine (demerol) distributed to a small number of IV-drug users in northern California. Four people developed persistent Parkinson-like symptoms soon after injecting the drug. Two years later, after the death of one of the patients due to a drug overdose, autopsy revealed marked degeneration of cells in the substantia nigra of the brain, similar to what is seen in Parkinson's disease. However, Lewy bodies were not identified in this patient or in several others who later were examined at autopsy after MPTP-induced parkinsonism. Laboratory animals, including nonhuman primates, treated with MPTP also develop Parkinson-like symptoms, and this has been used as a toxicant-induced animal model for studying the disease. Lewy bodies are missing in MPTP-treated animals as well, although degeneration of dopaminergic neurons in the substantia nigra is a universal finding.[19]

A "Risk Factor" Approach to PD

As a result of the MPTP observations, many epidemiologic studies have looked for influences of other environmental agents on Parkinson's disease risk. At the same time, studies in laboratory animals have validated findings of some of the epidemiologic investigations and clarified underlying mechanisms whereby environmental agents may cause Parkinson's disease

Here we review and summarize the results of investigations into the role of individual risk factors for Parkinson's disease but caution that it is highly unlikely that a single "smoking gun" will ever be identified as causing most cases of Parkinson's disease. The picture that emerges is one of multiple genetic and environmental variables in differing combinations that collectively influence risk. This means that, within any group of people with Parkinson's disease, the underlying collection of factors ultimately leading to their symptoms, diagnosis, and progression will vary considerably. That is, multiple different pathways and mechanisms can ultimately lead to Parkinson's disease or parkinsonism. It means that in most affected individuals there are multiple determinants of Parkinson's disease

risk, and within populations the causes of Parkinson's disease are heterogeneous. We will discuss the implications of this conclusion for individuals and public policy decision-making in chapter 9.



Potentially Protective Factors (Decreased Risk)

The single factor that is most consistently associated with a reduced risk of Parkinson's disease is cigarette smoking. A meta-analysis of case-control and cohort studies reported an approximate 60 percent reduction of Parkinson's disease risk in smokers, including a dose-response relationship (higher cigarette consumption over a longer time associated with lower risk).[20] Decreased risk is greater in current compared to former smokers. Pipe and cigar smoking and chewing tobacco also seem to be associated with lower risk although they have not been studied as thoroughly as cigarette smoking.[21]

Various biological mechanisms have been proposed to explain an apparent protective effect of smoking. In animal studies, nicotine seems to partially protect against pesticide-induced damage to dopaminergic neurons in the nigrostriatal region of the brain involved in Parkinson's disease.[22] But cigarette smoke contains hundreds of chemicals and others may be involved. Therapeutic trials of nicotine in patients with Parkinson's disease are underway. An early pilot study shows promising results but larger, randomized clinical trials will be necessary.[23]

The picture that emerges is one of multiple genetic and environmental variables in differing combinations that collectively influence risk.

Caffeine consumption is also associated with a reduced incidence of Parkinson's disease in many studies.[24] [25] A proposed mechanism involves the capacity of caffeine and related chemicals to block the activity of a neuromodulator, adenosine, in the brain.[26] In clinical trials, blocking adenosine has resulted in less severe muscle rigidity in people with Parkinson's disease as well as improved responsiveness to other therapies.

Hormone replacement therapy is inconsistently associated with a reduced incidence of Parkinson's disease in women.[27] [28] As with Alzheimer disease, the timing of hormone replacement therapy in relation to the timing of onset of menopause may influence impacts on Parkinson's disease risk.

Factors that Increase Parkinson's Disease Risk

Age, Gender

The single biggest risk factor for Parkinson's disease is advancing age. Incidence increases from about 17 cases per 100,000 person years between ages 50 and 59 to over 90 per 100,000 person years between ages 70 and 79.[29] Men have a significantly higher risk than women, although it remains unclear if this difference is due to inherent gender differences or differential exposure to environmental risk factors.[30] [31]

Pesticides

In the 1990s, two converging lines of evidence began to point toward the likelihood that exposure to pesticides could increase the risk of Parkinson's disease. First, a number of case-control epidemiologic studies concluded that rural living and drinking well water increased the risk of Parkinson's disease, but the evidence was inconsistent and its quality varied.[32] [33] In over 20 studies, when occupation was taken into account, farmers and other agricultural workers appeared to have an increased risk of Parkinson's disease. Those reports, of course, sparked concerns that agricultural chemicals might be responsible.

Epidemiologic Studies

A recent review of the peer-reviewed literature found that 24 of 31 studies, primarily of case-control design, reported an increased risk of Parkinson's disease associated with pesticide use.[34] In 12 of the 24 positive studies, the increased risk was statistically significant, with odds ratios ranging from 1.6 to 7.0. Only two of the 31 studies reported an odds ratio of less than 1.0. In the studies that attempted to distinguish among categories of pesticides, herbicides and insecticides were most likely to be associated with an increased risk. Of the 31 reviewed, all of the studies (6 of 6) that attempted to determine whether the risk of Parkinson's disease increased as pesticide exposure increased found a trend in that direction, and it was statistically significant in 4 of the 6.

As is often true of epidemiologic investigations, many of these studies have some limits. For example, most of them rely on participants' estimates of past pesticide use or exposure, which may or may not be valid. One study concludes, however, that this is unlikely to be a major issue for licensed pesticide applicators, who are generally able to recall and report valid information.[35] Many of the studies address pesticides as a class of chemicals and fail to identify individ-

ual chemical agents that may increase Parkinson's disease risk. This may not be a weakness. It is entirely plausible that different pesticides from different classes could increase risk through different as well as common mechanisms of toxicity.

Laboratory Animal Studies

A second line of evidence linking pesticides to Parkinson's disease risk comes from experimental laboratory work. After the MPTP discovery, further investigations showed that MPTP caused neurodegeneration in the substantia nigra at least in part through mitochondrial toxicity and free radical damage to dopaminergic neurons that seemed particularly vulnerable to this kind of insult. Some investigators turned their attention to the pesticides rotenone and paraquat because of their propensity to damage mitochondria and structural similarities to MPTP or its toxic metabolite, MPP+. This work provided a new model for studying cellular mechanisms that damage dopaminergic neurons.

Studies in rats showed that chronic intravenous administration of rotenone caused a Parkinson-like syndrome, damage to dopaminergic neurons in the substantia nigra, and cellular inclusions that look like Lewy bodies microscopically.[36] Studies also showed that paraquat caused a loss of dopaminergic neurons in laboratory animals.[37 38]

Maneb, a widely used dithiocarbamate fungicide, is another agricultural chemical also linked to Parkinson's-like symptoms in humans exposed during agricultural work,[39 40] in laboratory animals[41] and in cultures of dopaminergic cells from the brain.[42] A 1991 study reported that pre-treatment with a dithiocarbamate markedly boosted the adverse impacts of MPTP on locomotor activity and increased dopaminergic neuron damage in laboratory rodents.[43] This stimulated more research into the impacts of mixtures of agricultural chemicals.

Combinations of paraquat and maneb have been studied using a variety of dosing regimens. Scientists at the University of Rochester administered saline, maneb, paraquat, or maneb plus paraquat to mice. They showed that the combined exposure to paraquat and maneb caused synergistic decreases in motor activity and dopamine and increased damage to dopaminergic neurons in the striatal region of the brain.[44 45]

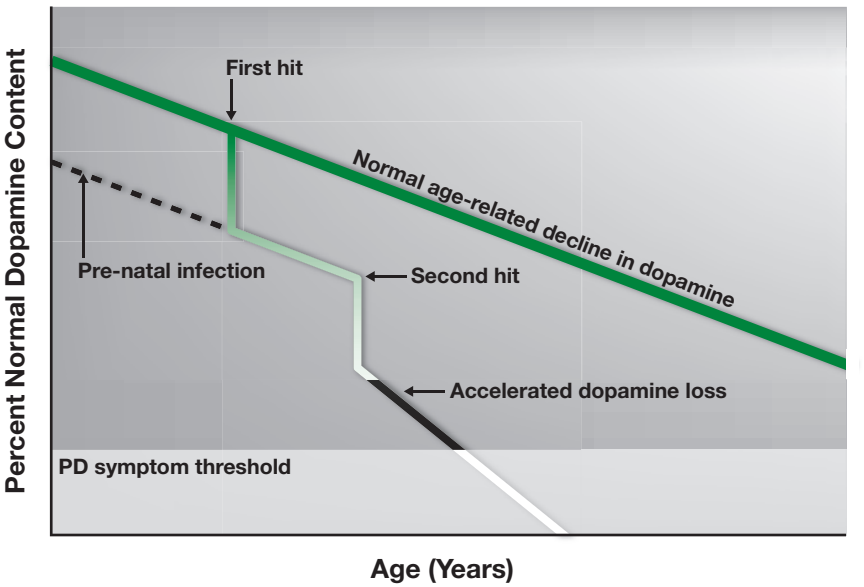
This team then explored the hypothesis that exposure to one or two of these chemicals during early development would increase susceptibility to exposures later in life. In one experiment, combined exposure to maneb and paraquat soon after birth produced loss of

dopamine and reduced numbers of dopamine neurons in the substantia nigra. Effects were greater than those produced by adult-only exposures. Moreover, combined exposures in infancy enhanced vulnerability to the same chemicals after exposure in adulthood.

In a second experiment, maneb exposures during fetal development markedly increased vulnerability to paraquat in adulthood, as measured by reductions in dopamine and numbers of dopaminergic neurons in the substantia nigra. Males were more vulnerable than females in both cases.[46] Other work in cell cultures had shown that paraquat caused oxidative damage by generating reactive oxygen species, while maneb interfered with regeneration of antioxidant defenses.[47]

In summary, these experiments showed the following: 1) Chemicals combined can act synergistically. That is, they can cause an enhanced effect that is greater than the sum of the effects of the individual chemicals. 2) Chemicals that cause toxicity through different mechanisms within the same system can have additive or synergistic effects. 3) Developmental exposures can "prime" the brain so that it is more susceptible to exposures that occur later in life. This is consistent with the concept of "multiple hits" that collectively, over time, result in clinical disease.

Multiple Hit Hypothesis



Early-onset or accelerated loss of dopaminergic cells caused by "hits" that may occur during fetal development and/or at any point throughout life ultimately result in sufficient loss of dopamine to cause clinical symptoms.

The herbicide paraquat and fungicide maneb are heavily used in large and often overlapping geographical areas with considerable likelihood of human exposures. Although investigators used intravenous exposures in the studies described above, follow-up studies in which paraquat was given to laboratory mice orally showed that the chemical was absorbed and transported to the brain with a half-life of one month.[48] Paraquat and maneb are absorbed after ingestion or inhalation and to some extent through dermal absorption in humans.[49] [50]

Additional Pesticides

Dieldrin is an organochlorine pesticide that is no longer manufactured or used in the U.S.. But traces of the chemical are still present in many humans and wildlife because it is persistent and bioaccumulative. An autopsy study found higher levels of dieldrin in the substantia nigra of ten Parkinson's disease patients compared to people without dementia and people with Alzheimer's disease.[51] The same study also found higher levels of lindane in the substantia nigra of people with Parkinson's disease. Lindane is another persistent, bioaccumulative pesticide that is still authorized for use in treating lice and scabies although alternatives exist. An earlier study detected dieldrin in 6 of 20 brains of people with Parkinson's disease, in 1 of 7 brains from people with Alzheimer's disease, and in none of 14 control samples. Since then, a number of in vitro and laboratory animal studies have attempted to elucidate mechanisms whereby dieldrin may increase the risk of Parkinson's.

In in vitro studies, dieldrin added to a preparation of alpha-synuclein protein markedly accelerates the development of protein aggregates similar to those seen in Lewy bodies.[52] Rotenone and paraquat have the same effect.

The ubiquitin-proteosome system (UPS) is another potential target for environmental agents associated with Parkinson's disease. The UPS is an intracellular mechanism that normally destroys proteins after they have served their purposes within the cell by shredding them into their component amino acids, which can then be recycled into new proteins.[53] Agents that impair the UPS may allow proteins such as alpha-synuclein, amyloid-beta, or others to inappropriately accumulate, increasing the risk of diseases associated with accumulation of those proteins. In in vitro experiments, rotenone, dieldrin, and two dithiocarbamate fungicides each impaired UPS functions at low concentrations.[54]

At low concentrations in cell culture systems, dieldrin also induces mitochondrial damage and microglial activation with release of reactive oxygen species causing oxidative stress, rapid release of dopamine, and apoptotic cell death.[55] [56] These effects also occur in intact laboratory animals at environmentally relevant levels of exposure.[57]

In another study, similar in design to those reported above with maneb, scientists fed dieldrin to female mice for three weeks at levels resulting in tissue concentrations similar to those found in people. The mice were then mated and their offspring studied after weaning. Male offspring that had been exposed to low-level dieldrin had a much larger decrease in nigrostriatal dopamine levels after MPTP exposure in adulthood than control animals. This once again demonstrates that perinatal exposures to toxic agents can prime the brain, making it more susceptible to further damage when challenged again in adulthood.[58] Female mice did not show the same dramatic drop in dopamine levels following MPTP, but perinatal dieldrin altered dopamine transport systems in both genders. The authors concluded that dieldrin had altered gene transcription activity at the DNA level, accounting for observed changes in levels of dopamine transport and packaging proteins.[c]

Finally, pyrethroids are another class of neurotoxic pesticides that deserve mention. They are usually divided into type I and type II based on their chemical structures. Pyrethroids are in widespread use, and their residues are commonly present in biomonitoring studies in the general population.[59] Several rodent studies have examined the impact of pyrethroids on dopaminergic systems in adults but few have examined developmental impacts. In one study, neonatal rats were given either pyrethrin (type I) or cypermethrin (type II) orally at 1/10 the LD50[d] daily from postnatal day 6 to 15.[60] They showed no gross evidence of toxicity or behavior changes. Activity levels were not different from controls at day 21 but by day 35, treated animals had increased levels of spontaneous activity. At day 35, dopamine content of the striatum was also significantly lower and evidence of oxidative stress was higher in treated animals compared to controls. Although no human data are available, this rodent study suggests that pyre-

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[c] *When the neurotransmitter dopamine is released into the synapse, it triggers a neuronal response. Dopamine is then transported back into the neuron by the dopamine transporter where it is repackaged into vesicles for subsequent use. If dopamine is not properly transported into the neuron or if transport into the neuron exceeds the rate of repackaging, excessive free dopamine may damage the neuron through oxidative stress. The concern is that perinatal exposures to certain chemicals, like dieldrin or PCBs, will permanently alter the dopamine regulatory system, making this part of the brain more vulnerable to additional challenges later in life.*

[d] *The LD50 is the dose that is lethal to 50% of the animals receiving that dose.*

throids, to which humans are commonly exposed, could be among the chemicals increasing the risk of Parkinson's disease by permanently down-regulating dopamine levels after developmental exposures.

In summary, despite remaining uncertainties and data gaps, the body of evidence linking pesticide exposure to Parkinson's disease fulfills generally accepted criteria for establishing causation. Epidemiologic studies show a fairly consistent association between pesticide exposure and increased Parkinson's disease risk, with an apparent dose-response pattern wherein larger exposures are associated with higher risk. These studies are consistent with extensive laboratory animal data, which also includes descriptions of underlying mechanisms of toxicity. Collectively, this evidence supports the conclusion that pesticide exposures can cause Parkinson's disease in some people.

Polychlorinated Biphenyls (PCBs)

Polychlorinated biphenyls (PCBs) are members of a class of persistent, bioaccumulative organochlorine chemicals historically used for many purposes, including as electrical insulators in transformers, lubricants, and paint additives. The EPA banned PCB manufacture in the U.S. in 1977 because of concerns about potential carcinogenicity. Since then, numerous studies have documented other adverse impacts on the development and function of the thyroid and nervous and immune systems.[61]

PCBs continue to contaminate the general environment and food chain. Biomonitoring studies detect PCBs in the vast majority of the U.S. population and levels increase with age.[62] In general, however, since the ban environmental concentrations and serum levels have been declining, although highly contaminated "hot spots" and disproportionately exposed individuals still exist.

Epidemiological and laboratory studies suggest that exposure to PCBs may be a risk factor for Parkinson's disease. A retrospective mortality study of over 17,000 workers occupationally exposed to PCBs reported an excess of Parkinson's disease–related deaths (nearly three times as many as expected) and dementia-related deaths (twice as many) in the women most highly exposed to PCBs but not in men.[63] This gender difference finding is surprising since men are generally at higher risk of idiopathic Parkinson's disease. Another postmortem study found higher levels of PCBs in the brains of people with Parkinson's disease than in controls.[64]

Animal studies show that some PCBs can reduce dopamine levels in the substantia nigra of nonhuman primates and rodents.[65] [66]

One plausible mechanism whereby PCBs may reduce dopamine and increase the risk of Parkinson's disease involves the induction of prolonged oxidative stress in dopaminergic neurons.[67 68 69] In vitro studies show that PCBs facilitate prolonged up-regulation of heme oxygenase levels and release of iron, contributing to oxidative stress and cell damage.[70] In these studies, iron chelation and blocking the rise in heme oxygenase reduced the impacts of PCBs.

Another plausible mechanism whereby PCBs may increase Parkinson's disease risk involves changes to the dopamine transporter system. Mice exposed to PCBs at levels resulting in tissue levels similar to those in the post-mortem brains of people with Parkinson's disease showed a significant decrease in both the transporter protein and repackaging protein.[76] (See footnote c.) The authors propose that failure to repackage dopamine normally sets the stage for prolonged dopamine-related oxidative stress.

Solvents

Organic solvents are used in industry for cleaning, degreasing, extraction, surface coating, and laboratory work. They are components of paints, inks, glues, adhesives, and hydrocarbon fuels. The main route of exposure is through inhalation. Long-term exposures can be neurotoxic, causing peripheral neuropathies and central nervous system symptoms such as mood swings; depression; headache; and impaired cognition, concentration, and memory.[77]

Different solvents, including carbon disulfide, methanol, n-hexane, and trichloroethylene (TCE), have been reported associated with parkinsonism, although exposures to mixtures are more commonly identified in studies showing a significant relationship.[78-82] The central nervous system damage associated with solvent exposures includes the substantia nigra, but other areas of the brain are often involved.

A recent report of two cases of acute onset of parkinsonism after ingestion of ethylene glycol or methanol in suicide attempts described hemorrhagic necrosis in the basal ganglia of the brain.[83] The involved area is intimately interconnected with the nearby substantia nigra and plays a role in classic Parkinson's disease. The nature of the damage described in these two cases, however, differs from classic Parkinson's disease despite the similarities of neurological symptoms.

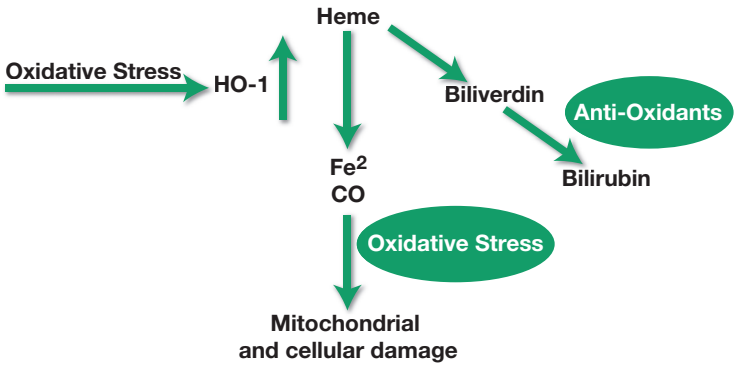
How *it* Works

Heme Oxygenase

Heme oxygenase 1 (HO-1) and heme oxygenase 2 (HO-2) are normally occurring enzymes that can be induced by oxidative stress and other noxious stimuli. Although present in many tissues, HO-1 is normally present in the brain at very low levels compared to HO-2. These enzymes facilitate the degradation of heme proteins (responsible for oxygen transport in red blood cells, among other functions), producing biliverdin, bilirubin, and low levels of carbon monoxide (CO).

At low levels, CO is neuroprotective*, and biliverdin and bilirubin have strong antioxidant properties. But free iron, which is also generated, combines with naturally occurring hydrogen peroxide to generate the highly reactive hydroxyl radical and is therefore a source of oxidative stress.

This system is generally thought to have protective effects by increasing the antioxidant capacity of cells. Recent data suggest, however, that chronic overproduction of HO-1 may actually increase rather than decrease oxidative stress by generating excessive iron.[71 72 73] HO-1 and iron are present in the substantia nigra at higher levels in people with Parkinson's disease than in controls. HO-1 is also present at higher levels in the hippocampus of people with Alzheimer's disease compared to controls.[74]



Some neuroscientists propose that the heme oxygenase system, which normally has a neuroprotective function, may, under certain circumstances, actually increase oxidative stress and cell death by generating excessive amounts of free iron, a powerful oxidant.

**High levels of CO exposure as may be caused by CO poisoning from an outside source may cause brain damage and symptoms of parkinsonism.[75] Brain imaging studies after CO poisoning show widespread damage of white matter and the basal ganglia.*

Another recent report describes parkinsonism in 30 workers associated with long-term occupational exposure to TCE.[84] In an accompanying study, adult male rats dosed orally with 1000 mg TCE/kg body weight five days a week for six weeks developed mitochondrial damage and dopaminergic neuron loss in the substantia nigra. Alpha-synuclein inclusions were present in the substantia nigra and dorsal motor nucleus of the vagus nerve in treated animals.

TCE is a particular concern not only because of frequent use as a degreasing agent in industry but also because it is a frequent surface- and groundwater contaminant resulting in widespread, low-level exposures in the general population.[85] One of the metabolites of TCE, chloral hydrate, can combine with tryptamine, a normally occurring chemical that serves as a backbone for a number of biologically active compounds, to form TaClo.[e] Structurally, TaClo resembles MPTP, easily crosses the blood-brain barrier, and causes neurodegeneration and Parkinson-like symptoms in animal tests.[86] [87] The clinical relevance of this mechanism and the influence of low-level exposures to TCE on Parkinson's disease risk in the general population are unknown.

Metals

Exposures to metals, such as lead, manganese, iron, copper, and others, have been of interest since some occupational studies identified them as potential risk factors for Parkinson's.[88] [89] [90] [91] Mechanisms whereby metals may influence Parkinson's disease risk include increased oxidative stress and facilitation of protein aggregation. Even without excessive exposures, however, abnormal transport of essential metals such as copper, zinc, or iron into the brain or mishandling of the metal within the brain may trigger these responses.[92] The following discussion will focus primarily on the potential influence of exogenous sources of metals on Parkinson's disease risk.

Manganese

Manganese is a micronutrient required in a number of normal enzymatic processes, but excessive exposures can be harmful. Whereas dietary levels may vary considerably, in adults homeostatic mechanisms regulate manganese absorption and excretion, thereby maintaining optimal levels. Various mechanisms are responsible for transporting manganese across the blood-brain barrier.[93] For example, manganese can attach to an iron-transporter protein to

[e] *1-trichloromethyl-1,2,3,4-tetrahydro-β-carboline*

cross the blood-brain barrier, and when iron stores are deficient, brain levels of manganese increase. Unbound manganese can also gain access to the brain. Studies in rodents show that homeostatic mechanisms are not fully developed in infancy, and dietary manganese supplements result in elevated levels in the brain and decreased dopamine in the nigrostriatal system.[94]

Soy infant formula contains about 200–300 micrograms of manganese per liter. Cow's milk formula contains 50–100 micrograms of manganese per liter and human milk about 3–8 micrograms per liter.[95] Although in animals, manganese absorption is lower from soy formula than from milk formula or breast milk, manganese retention is quite high.[96] Studies in term and pre-term infants also show high retention of manganese.[97] Formula-fed infants have significantly higher manganese levels in their hair at four months than breastfed infants, indicating higher absorption and retention.[98] Initial studies of neurodevelopment in children exposed to high levels of manganese in drinking water (greater than 300 micrograms per liter) show impairments in intellectual function.[99] It is entirely plausible that excessive dietary manganese exposures in infant humans will result in higher brain levels of manganese and increase the risk of neurodegenerative diseases later in life, but this has never been studied.

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Occupational studies show that miners can be exposed to elevated levels of manganese, primarily by inhalation, and they are at risk for movement disorders resembling Parkinson's disease although other features of their illness differ.[100] [101] Despite some clinical similarities, pathologic studies of brain tissue after excessive manganese exposure in adulthood show that an important part of the basal ganglia known as the globus pallidus is the most prominently damaged, with relative sparing of the substantia nigra and an absence of Lewy bodies.[102]

Studies of metal welders who may also be exposed to manganese by inhalation have been inconsistent with respect to risk of Parkinson's disease. An extensive recent review concludes that many of the available studies are limited by methodologic issues such as lack of accurate exposure data, inadequate control groups, or case selection bias.[103] These limitations make it difficult to determine whether welders are at increased risk of neurological effects and if they are,

whether manganese is responsible. Although existing studies do not provide compelling evidence of increased risk of Parkinson's disease or parkinsonism among welders, the database is not sufficiently robust to justify dismissing the possibility, particularly in highly exposed or otherwise susceptible individuals.

Two additional potential sources of manganese exposure by inhalation in the general population deserve mention. Methylcyclopentadienyl manganese tricarbonyl (MMT) added to gasoline as an octane enhancer may cause elevated levels of manganese in particulate air pollution. The Ethyl Corporation, which manufactured tetraethyl lead as a gasoline additive until its use was banned in the U.S. and many other countries, is promoting MMT as an alternative. After Ethyl Corporation's legal challenges in response to proposed bans, MMT is permitted as a gasoline additive but is reportedly not being used by any major gasoline manufacturer in the U.S.[104]

In Canada, MMT use in gasoline has been common. Although environmental levels of manganese are higher in high-traffic than in low-traffic areas, blood levels of manganese in people do not significantly differ between the two.[105] Studies in rodents and fish, however, show that manganese can travel directly into the brain from the nose along the olfactory nerve.[106] Whether this occurs in people to any appreciable extent is unknown.

Emissions from steelmaking industries are a second potential source of population-wide manganese exposures. A study in the steelmaking city of Hamilton, Ontario, reported an increased risk of Parkinson's disease associated with increases in manganese content in particulate air pollution.[107] If the finding is valid, it may represent either an increase in manganese-related parkinsonism or acceleration of the onset of true Parkinson's disease, consistent with the theory that manganese further promotes the loss of dopaminergic neurons attributable to natural aging.[108]

Iron

Dietary iron is essential for a number of vital enzymatic processes throughout the body, including the brain, and as a component of hemoglobin in red blood cells. Normal myelination, neuron and synapse formation, and neurotransmission are highly dependent on normal iron availability. Excessive iron, however, can be toxic to cells. Iron increases levels of oxidative stress in the brain by contributing to

the formation of free radicals. It contributes to mitochondrial dysfunction, and in people with Parkinson's disease may promote the formation of Lewy bodies by enhancing alpha-synuclein aggregation.[109]

As a result of iron's essential but potentially toxic role in brain development, function, and aging, scientists investigating both neurodevelopment and neurodegeneration have extensively studied this metal. We do not intend to review this large literature here but rather to summarize findings related to potential neurodegenerative effects of excessive dietary iron, while explicitly recognizing the essential role of iron in normal brain development and function.

Dietary Iron—Infants and Children

Iron absorption, excretion, and metabolism are tightly regulated in most tissues, including the brain. It is well established that iron tends to accumulate in the substantia nigra and elsewhere in the basal ganglia in all people, beginning in childhood. An imaging study of normal children shows that brain iron accumulation begins sooner and is more extensive in some than in others, but the reasons are unknown.[110] Over time, people who develop Parkinson's disease tend to accumulate higher levels of iron in the substantia nigra for reasons also not well understood, although chronic oxidative stress may play a role.[111] (See the heme oxygenase sidebar.)

Most investigators believe that this iron comes primarily from endogenous sources and not from excessive iron exposure. One theory holds that excessive iron deposition in the substantia nigra of people with Parkinson's disease is the result of genetic variations in iron regulatory proteins.[112] Some evidence, however, suggests that this excess iron may not entirely result from endogenous sources. Studies in rodents, for example, demonstrate the following:

- Elevated dietary iron levels during the newborn period (up to three weeks) permanently increased brain iron levels and caused dopaminergic neurodegeneration in adulthood. Moreover, elevated dietary iron in newborn mice resulted in profoundly increased susceptibility to MPTP-induced neurodegeneration in adulthood. The dietary levels of iron used in this study (of mice) were comparable to the levels in fortified human infant formula.[113]
- Iron sequestered in the brain during infancy tends to stay there although it may be redistributed (according to a rat study).[114] Even an iron-deficient diet during adulthood does not mobilize previously deposited iron from the brain (rat).[115]

Taken together, these studies make a strong case that both too little and too much dietary iron during infant and child development can be harmful.

These results suggest that excessive dietary iron, beginning in infancy, could increase the risk of neurodegenerative diseases later in life.

Iron levels in human milk are fairly tightly regulated and largely independent of maternal iron status.[116 117] Breast milk iron levels are about 1 mg/L at birth and fall to about 0.3 mg/L at six months. Similarly, lactoferrin, a breast milk protein that plays a role in regulating the absorption of iron from the infant intestinal tract, is highest at birth and declines thereafter.

Infant formulas not fortified with iron contain about 2 mg iron/L. Fortified formulas in the U.S. can contain as much as 12 mg iron/L. Iron derived from infant formula is generally not accompanied by lactoferrin and is in a different form from iron in breast milk. As a result, iron in formula is not as well absorbed from the intestine as iron from breast milk. Nevertheless, absorption of iron supplements is not well regulated in the young infant and can be excessive if dietary levels are high.[118]

Excessive iron supplementation in the young infant can have adverse impacts on development if the child is iron replete.[119] Whether excessive dietary iron supplementation in human infants results in excessive brain deposition of iron is unknown. Recently, Betsy Lozoff from the University of Michigan reported for the first time that a group of children who had high hemoglobin levels at six months of age and were fed infant formula fortified with iron at 12 mg/L performed more poorly on tests of spatial memory, motor coordination, and overall visual-motor coordination.[120] This suggests that excessive iron may actually have adverse impacts on neurodevelopment in infants who already have adequate iron stores.

On the other hand, iron deficiency is the most common nutritional deficiency in the U.S. and throughout the world. It is associated with delayed neurological development including cognitive deficits. Iron deficiency in infancy may also increase the risk of neurodegenerative disease later in life. In a recent animal study, iron deficiency during development altered the expression of a number of genes in the developing hippocampus, including up-regulating several genes involved in Alzheimer's disease.[121]

Taken together, these studies make a strong case that both too little and too much dietary iron during infant and child development can be harmful. Excessive dietary iron from highly fortified infant formulas may not only adversely impact neurodevelopment in some children but also increase the risk of neurodegenerative diseases in adulthood, particularly in the context of additional sources of oxida-

tive stress. For non-breastfeeding children, the American Academy of Pediatrics strongly recommends the use of formula fortified with iron at levels between 4 and 12 mg/L. Within this range, however, there remains considerable uncertainty and debate about optimal levels.[122]

Dietary Iron—Adults:

Several case-control studies in adults, using dietary questionnaires to estimate exposure levels, have looked for links between dietary iron and Parkinson's disease risk. In a study of 250 people newly diagnosed with Parkinson's disease and 388 control subjects in which participants attempted to reconstruct dietary patterns over their lifetime, those with the highest dietary iron intake from supplements or multivitamins had a 70 percent increased risk of Parkinson's disease compared to those with the lowest intake.[123] A combined above-average intake of iron and manganese was associated with a doubling of Parkinson's disease risk.

In another study of 126 people with Parkinson's disease and 432 controls, in which a one-year retrospective history was used to estimate dietary patterns, those with the highest intake of iron had a near doubling of Parkinson's disease risk (OR 1.94; 95% CI 1.05-3.58).[124] A third study of 104 patients and 352 controls using dietary questionnaires found no association with dietary iron from food or supplements.[125]

In people with Parkinson's disease considerable uncertainty remains about whether iron deposition is an important contributor to dopaminergic neuron destruction or, rather, a manifestation of the disease. The most commonly held view emphasizes that iron deposition increases oxidative stress, contributing to dopaminergic neuron loss, and iron deposition increases as the disease progresses—creating a positive feedback loop. In summary, combinations of excessive iron intake, excessive deposition, and abnormal iron regulation are likely to influence the onset and progression of pathogenic processes in the areas of the brain affected in Parkinson's disease.

Lead

Many studies of lead exposure as a risk factor for Parkinson's disease have been limited by inadequate exposure assessment. Questionnaires, job histories, and blood lead levels are poor substitutes for quantifying actual exposure levels over time. A recent case-control study of 121 people with Parkinson's disease and 414 controls used bone lead measurements (via X-ray fluorescence technology), which

Particulate air pollution is likely to be a risk factor for both Alzheimer's disease and Parkinson's disease.

give an assessment of cumulative exposures over time. It found that the risk of Parkinson's disease was significantly elevated by more than two-fold in people in the highest quartile of lead exposure when compared to the lowest quartile.[126] The findings were modified to some degree when age was accounted for, but age did not fully explain the increased risk. The authors concluded that occupational lead exposure is a risk factor for Parkinson's disease. The mechanism(s) by which heavy metals, including lead, may increase Parkinson's disease risk include increasing oxidative stress, lipid peroxidation of cellular membranes, and abnormal folding of alpha-synuclein protein.[127] [128]

Air Pollution and Food Contaminants

Recent studies in laboratory animals and humans show that particulate air pollution increases markers of oxidative stress and inflammation in the brain and is associated with abnormal deposition of amyloid and alpha-synuclein.[129] [130] Particulate air pollution is likely to be a risk factor for both Alzheimer's disease and Parkinson's disease. This is discussed in more detail in chapter 7.

In recent years, indoor air pollution has also received much needed attention as a source of potentially harmful exposures. Depending on building design, operations, and furnishings, indoor air can be contaminated with a complex mixture of chemicals, which can, in turn, react with each other to form novel compounds.

No studies have specifically linked indoor air pollutants with Parkinson's disease or Alzheimer's disease. However, the type-2 alkenes, a group of chemicals to which people are commonly exposed occupationally, in indoor and outdoor air, and through dietary contamination, are receiving attention as potential sources of oxidative stress in the brain affecting large numbers of people.[131] Acrolein and 4-hydroxy-2-nonenal are two members of this class of chemicals that are also generated endogenously when lipids are damaged by oxidative stress. These two chemicals, in turn, add additional oxidative stress themselves and are hypothesized to damage synapses, ultimately resulting in neuronal death. Increasingly, neuroscientists are

considering their potential for playing a role in Alzheimer's disease and Parkinson's disease.

In addition to endogenous sources, however, some type-2 alkenes are used extensively in manufacturing, agriculture, and the chemical industry and are common environmental contaminants. Acrolein, for example, is present in both indoor and outdoor air, commonly at levels that exceed safety thresholds.[132] Outdoor sources of acrolein include incomplete products of fuel combustion and forest fires. Indoor sources include cigarette smoke, cooking fuels, and oxidation of emissions of volatile organic compounds from building materials and furnishings.

Acrylonitrile, also a type-2 alkene, is a high volume chemical used in the manufacture of textiles, nitrile rubbers, and plastics. It is also a chemical intermediate in the manufacture of dyes and pharmaceuticals. Type-2 alkenes acrylamide and methyl acrylate are common dietary contaminants.[133] Acrylamide, a carcinogen and neurotoxicant, is formed when carbohydrate-rich foods are cooked at high temperatures.

The concern is that widespread environmental exposures to type-2 alkenes will add significantly to the impacts of those produced endogenously, increasing oxidative stress in the brain and thereby, the risk of Alzheimer's disease and Parkinson's disease. At the moment, however, the public health implications of exposures to this class of chemicals are unknown.

Infectious Agents

In 1917, von Economo described a disease that emerged during and after pandemic influenza swept through Europe.[134] He named it encephalitis lethargica because many of its victims experienced extreme lethargy, often associated with abnormal eye movements. In some people rigidity was prominent, and von Economo remarked on the clinical resemblance to parkinsonism. Later, he began reporting cases with features of parkinsonism that suddenly appeared years after the initial illness of influenza had completely cleared, whether it had been accompanied by encephalitis or not.

Except for rare cases, searches for other infectious agents that may be responsible for parkinsonism have not been productive. Several more recent discoveries, however, rekindle interest in the possibility that infections may increase risk. They come from new models for studying Parkinson's disease and may help to explain variable susceptibility to environmental triggers.

Lipopolysaccharide (LPS) is the major component of the cell wall of gram negative bacteria. As discussed in chapter 6, LPS triggers the innate immune system by interacting with the Toll-like receptors (TLR), initiating a pro-inflammatory response cascade. Laboratory studies in rodents show that, compared to controls, exposure to LPS during pregnancy results in offspring with lower levels of brain dopamine, fewer dopaminergic neurons in the substantia nigra, Lewy body–like structures in the brain, increased levels of pro-inflammatory markers, and microglial activation.[135] [136] Prenatal LPS exposure also permanently lowers antioxidant levels in the brain and renders animals more susceptible to secondary challenges to neurotoxicants in adulthood.[137] For example, prenatal exposure to LPS followed by intravenous exposure to rotenone in adulthood causes a synergistic loss of dopaminergic cells and dopamine levels in the substantia nigra.[138] Even adult mice given a single injection of LPS develop prolonged activation of microglia and progressive loss of dopaminergic neurons in the substantia nigra that continues long after LPS exposure.[139] These studies support the idea that certain bacterial infections may increase the risk of Parkinson's disease through several mechanisms.

Finally, a recent study examined the impact of extremely low levels of formyl-methionyl-leucyl-phenylalanine (fMLP) on microglia and dopaminergic cells in tissue cultures from the brain of rodents.[140] fMLP is a chemical produced by bacteria as they invade and damage tissue. It is a chemo-attractor, guiding white blood cells and other cells involved in the inflammatory response to the site of an infection. The authors of the report decided to study fMLP because of its structural similarity to an endogenous compound in the brain that can activate microglia (substance P). They found that extremely low levels of fMLP activated microglia in the tissue culture and caused marked dopaminergic cell loss. This observation raises the interesting possibility that the body's response to a number of different infections could "prime" the substantia nigra by activating microglia. It will require confirmation and further study in intact laboratory animals in order to judge its relevance to Parkinson's disease risk in humans.

Dietary Risk Factors

Diet may play a role in the origins of Parkinson's disease by altering the oxidative balance in the brain, by otherwise increasing or decreasing susceptibility to neurotoxicants, or as a source of neurotoxic agents. But studying the impact of diet in people presents

several challenges. First, investigators commonly use dietary recall or food frequency questionnaires to identify eating habits of study participants. Even when the questionnaires are carefully designed, the risk of inaccurate recall is always a concern that grows with increasing length of time of interest. This is a significant limitation for Parkinson's disease, which usually has an insidious onset of symptoms and a long pre-clinical latency period. Recent dietary history may not be as relevant as eating habits long ago—even as far back as early development.

Recent dietary history may not be as relevant as eating habits long ago—even as far back as early development.

A second limitation comes from considering the diet be a collection of individual foods or nutrients rather than as an integrated whole. Single nutrient deficiencies (e.g. a vitamin) or excesses (e.g. saturated fat) may be relevant, but focusing entirely on specific foods ignores biologically relevant interactions among nutrients, increasing the likelihood of inconsistent, conflicting, or even misleading conclusions. Alternative approaches, such as dietary pattern analysis, can help to address this problem.[141 142]

Table 1 summarizes the findings of available epidemiologic studies examining the influences of diet on Parkinson's disease risk. Study sizes and designs differ, including methods for controlling for covariates, effect modifiers, and confounders.

Three large prospective cohort studies find an increased risk of Parkinson's disease with increased intake of milk. A meta-analysis of these three studies[156] found a 60 percent increased risk in people who consume the largest amount of milk when compared to those who consume the least (80% increased risk for men; 30% increased risk for women). The reason for this increased risk is not clear, but it does not appear to be related to dairy fat or calcium. Hypotheses include the potential presence of neurotoxic agents in the milk, for example, pesticides, [157 158] and decreased uric acid associated with increased dairy product intake.[159]

The studies also suggest reduced Parkinson's disease risk with higher intake of dietary vitamin E. Increases in dietary unsaturated fatty acids may also decrease risk. As mentioned previously, two of three case-control studies found an increased risk of Parkinson's disease with increased dietary iron.

The single study employing dietary pattern analysis found reduced risk with a diet rich in fruits, vegetables, nuts, legumes, and fish and low in saturated fat. Such a diet would contain abundant antioxidants and be less likely to stimulate a general inflammatory response. (See chapters 6 and 7.)

Table 1: Diet and Parkinsons's Disease Risk

Study	Study type	Sample size	Dietary features analyzed	Results
Etminan, 2005[143] (includes Zhang, 2002)	Meta-analysis of 6 case-control, 1 cohort, 1 cross-sectional studies		Vitamins E, C, beta-carotene	Dec. risk of Parkinson's disease with inc. dietary vitamin E
Chen, 2004[144]	Prospective cohort	47,341 men 88,716 women	Folate, vit B6, vit B12	No effect
Chen, 2002[145]	Prospective cohort	47,331 men 88,563 women	Food groups	Inc. risk of Parkinson's disease with higher intake of dairy products in men; not in women
Chen, 2007[146]	Prospective cohort	57,689 men 73,175 women	Dairy products	Inc. risk of Parkinson's disease with inc. intake of dairy products, mostly explained by milk intake
Zhang, 2002[147]	Prospective cohort	47,331 men 76,890 women	Foods rich in vitamins E, C, carotenoids; vitamin supplements	Dec. risk of Parkinson's disease with vit. E-rich foods but not supplements; dec. risk with nuts
Gao, 2007[148]	Prospective cohort	46,692 men 81,676 women	Principal component analysis to identify dietary patterns	Dec. risk of Parkinson's disease with diet rich in fruits, vegetables, legumes, nuts, fish; low in sat'd fat
De Lau, 2005[149]	Prospective cohort	7,983	Total energy, total fat, sat'd FA, trans FA, cholesterol, MUFA, PUFA, carbohydrates, dairy, alcohol, vit E, coffee (beginning one year prior to onset of study; 6 yr follow up)	Dec. risk of Parkinson's disease with higher intake of total fat, MUFA, PUFA; no assoc with sat'd FA, cholesterol, trans FA
De Lau, 2006[150]	Prospective cohort	5,289	Dietary folate, vit. B6, vit. B12	Dec. risk of Parkinson's disease with higher intake of B6; no assoc. with folate, B12
Park, 2005[151]	Prospective cohort	7,504 men	Milk; dietary calcium (at the time of study initiation; follow up over 30 yrs.)	Inc. risk of Parkinson's disease with inc. milk intake; no assoc. with calcium
Logroscino, 1998[152]	Case-control	104 cases 352 controls	Dietary iron, animal fat	No effect of dietary iron; inc. risk of Parkinson's disease with animal fat intake in people with low transferrin saturation*
Powers, 2003[153]	Case-control	250 cases 388 controls	Food freq. habits for most of adult life	Inc. risk of Parkinson's disease with high iron intake; higher risk with high iron and manganese intake; no assoc. with fat
Johnson, 1999[154]	Case-control	126 cases 432 controls	Estimates of foods eaten in past year	Inc. risk of Parkinson's disease with high intake of total fat, sat'd fat, cholesterol, lutein, iron
Gao, 2008[155]	Prospective cohort	47,406 men	Foods that influence blood uric acid level	Dec. risk of Parkinson's disease with inc. intake of foods that raise uric acid levels

**This suggested to the authors that dietary fat and abnormal iron metabolism might interact to increase Parkinson's disease risk*

Three large prospective studies and one case-control study found that lower plasma uric acid levels are associated with an increased risk of Parkinson's.[160] [161] [162] [163] A meta-analysis of the three prospective studies concluded that a 1.32 mg/dl increase in plasma urate was associated with an approximate 20 percent decreased risk of Parkinson's disease. This is plausibly a causal relationship since uric acid is a strong antioxidant, and oxidative stress in the brain is likely to play a major role in the etiology of Parkinson's disease.

A prospective cohort study of over 47,000 men concluded that higher intake of foods that increase blood levels of uric acid result in a decreased risk of Parkinson's disease.[164] [f] This relationship remained significant after controlling for smoking, coffee consumption, body mass index, and total caloric intake.

Finally, an animal study examining the impact of polyunsaturated fatty acids on susceptibility to MPTP-induced nigrostriatal damage deserves mention.[165] For ten months investigators fed one group of mice a diet enriched with omega-3 fatty acids so that the omega-6:omega-3 fatty acid ratio was 1.19. They fed a second group a diet with an omega-6:omega-3 fatty acid ratio of 101:1. Each diet contained equal calories per gram and equal percentages of proteins, fats, and carbohydrates. However, the high omega-6 fatty acid diet was completely devoid of the omega-3's eicosapentanoic acid (EPA) and docosahexanoic acid (DHA). After ten months some of the mice were given intraperitoneal injections of MPTP at doses known from previous studies to cause moderate damage to dopaminergic cells. When the brains were examined two weeks later, the omega-3 fatty acid–enriched diet had completely blunted the loss of dopaminergic neurons in the substantia nigra caused by MPTP. In the striatum, dopamine levels were significantly preserved in the group given the omega-3–enriched diet. This dramatic protective effect led the authors to conclude that low human consumption of omega-3 fatty acids might be an important modifiable risk factor for Parkinson's disease. It is worth noting that this is different from concluding that excessive omega-6 fatty acids are responsible for the increased susceptibility. Both omega-6 and omega-3 fatty acids are essential in the diet, but high levels of dietary omega-6s combined with inadequate levels of omega-3s can result in an excessive inflammatory response. (See chapter 6.)

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[f] *The authors derived a dietary urate index by assessing intake of the following foods and nutrients: meat, seafood, dairy protein, individual dairy foods and dairy products, alcohol, vitamin C, fructose, sucrose, vegetables, legumes and soybean products, flavonoids, folate, coffee, caffeine. Some of these tend to increase uric acid levels (e.g. meat, fructose, alcohol) and others tend to lower levels (dairy proteins, vitamin C).*

In summary, available epidemiologic and laboratory animal data indicate that the risk of Parkinson's disease can be influenced by diet. The weight of evidence points to an increased risk, primarily in men, with increased consumption of dairy products. Increased iron intake also appears to increase Parkinson's disease risk although the evidence is more limited. Foods rich in antioxidants and polyunsaturated fatty acids and foods that increase uric acid levels are likely to decrease risk. Among the polyunsaturated fatty acids, an increase in omega-3 fatty acids may be particularly useful.

Obesity, Body Mass Index as Risk Factors

Available epidemiologic and laboratory animal data indicate that the risk of Parkinson's disease can be influenced by diet.

The results of prospective studies of the influence of obesity or body mass index on Parkinson's disease risk are inconsistent. Table 2 summarizes the available data. Although it is tempting to hypothesize a connection among obesity, higher intake of dietary fat, and increased Parkinson's disease risk, it must also be noted that dopamine plays an important role in appetite regulation and energy metabolism. Obesity is also associated with decreased dopamine (2) receptors in the brain, which may in turn influence dopamine levels and turnover.

Obesity could also influence the effect of other Parkinson's disease risk factors. For example, in a study in mice, obesity was induced by adding beef tallow to the diet.[166] Obese and lean control animals were then exposed to low and high doses of MPTP. Obese

Table 2: Obesity/BMI and Parkinson's Disease Risk

Study	Study type	Sample size	Measurement	Results
Abbott, 2002[167]	Prospective cohort	7,990 Japanese-American men	Triceps skin fold thickness	Inc. Parkinson's disease risk with inc. triceps skin fold thickness
Chen, 2004[168]	Prospective cohort	47,700 men 117,062 women	Baseline BMI; waist circumference; waist-hip ratio	Parkinson's risk not assoc. with BMI; inc. risk of Parkinson's with inc. waist circumference and waist-hip ratio in never-smokers only
Hu, 2006[169]	Prospective cohort	22,367 men 23,439 women	Baseline BMI	Inc. Parkinson's disease risk with inc. BMI in men and women

animals had higher levels of oxidative stress and inflammatory markers than control animals. Obese animals experienced a much greater decline in dopamine levels in the striatum than lean animals after MPTP exposure, even though the toxic metabolite of MPTP, MPP+, was present in equal amounts in the striatum of both groups. The authors concluded that the neurodegenerative effects of MPTP were enhanced by obesity.

Head Trauma

Studies examining head trauma as a risk factor for Parkinson's disease have produced inconsistent results, but here again, long latencies and other study design issues are challenging to address. Case-control studies can be limited by recall bias; that is, people with Parkinson's disease may be more likely than controls to recall past head trauma. Other variables may confound the relationship. For example, genetic makeup could influence risk-taking behavior or personality type, which might be related to head trauma risk. Yet, Parkinson's disease as an outcome of repeated head trauma, as in boxers, is well known.

At least two mechanisms other than direct injury to neurons in the substantia nigra could plausibly increase risk. The blood-brain barrier could be disrupted by head injury, allowing neurotoxic agents to gain access to the brain. Or, trauma could initiate an inflammatory response that does not fully resolve, ultimately resulting in clinically significant loss of dopaminergic neurons decades later.

Of nine published retrospective case-control studies, five showed a significantly positive association between past head trauma and Parkinson's disease, two showed a positive association that was not statistically significant, and two were negative.[170] [171] One prospective nested case-control study, in which the history of head trauma was obtained before the onset of symptoms of Parkinson's disease, found a four-fold increased risk.[172] A study of twins in which one had Parkinson's disease and one did not found that previous head trauma was positively associated with the disease, and the risk was greater with more severe or repeated trauma.[173]

Summary

Various combinations of genetic and environmental factors are likely to explain most cases of Parkinson's disease. Distinctions between classic Parkinson's disease and other forms of parkinsonism are not always clear. Loss of dopaminergic neurons and their influences on other neuronal circuits are responsible for the most commonly recognized motor features of Parkinson's disease. But the pathology of Parkinson's disease is not confined to the brain and, in fact, some of the earliest changes may begin completely outside of the central nervous system, long before clinical symptoms appear. A range of timeframes may precede the development of clinical symptoms, including neurotoxic insults as far back as early development.

Different mechanisms may reduce dopaminergic function in Parkinson's disease. Oxidative stress is a common finding but whether it is essential early in the development of Parkinson's disease or a later phenomenon following other triggers is uncertain. Nevertheless, virtually all environmental factors associated with increased risk also increase oxidative stress, to which the substantia nigra and its dopaminergic system are particularly vulnerable. Other relevant mechanisms include combinations of abnormal alpha-synuclein deposition, mitochondrial dysfunction, proteosome dysfunction, inflammation, and DNA damage. These mechanisms are not independent and unrelated. Rather, interactive, evolving feedback loops consisting of combinations of mechanisms are likely to influence the onset and progression of disease. Each of these mechanisms can be set in motion by environmental factors.

Table 3 lists Parkinson's disease risk factors discussed in this chapter. But, they do not exist in isolation. Most people experience them in interactive combinations. Their timing varies and impacts may be additive or synergistic, as described in the "multiple hit" model. Together they create conditions in which susceptibility is increased or decreased. For example, animal studies show that diet-induced obesity increases susceptibility to MPTP-induced neurodegeneration whereas an omega-3 fatty-acid enriched diet is protective. Prenatal exposures to maneb or lipopolysaccharide prime the brain to be much more susceptible to neurodegenerative damage from pesticides in adulthood.

Given the growing list of risk factors for Parkinson's disease and long latency periods between relevant exposures and clinical symptoms, studying them collectively becomes a nearly insurmount-

Table 3: Environmental risk factors for Parkinson's disease or parkinsonism discussed in this chapter*

Increased risk potential:

- Pesticides
- PCBs
- Solvents
- Dietary iron
- Manganese
- Lead
- Carbon monoxide
- Diet rich in dairy products
- Obesity
- Lipopolysaccharide
- Head trauma
- Air pollution
- Type-2 alkenes
- Infections

Decreased risk potential:

- Diet rich in polyunsaturated fatty acids
- Diet rich in antioxidants
- Diet rich in foods that raise uric acid levels
- Coffee drinking
- Cigarette smoking

**strength of evidence varies*

The pathology of Parkinson's disease is not confined to the brain and, in fact, some of the earliest changes may begin completely outside of the central nervous system, long before clinical symptoms appear.

able challenge. Imagine the difficuties inherent in studying the combined impacts of lifelong diet—including excessive dietary iron in infancy and adulthood, dairy products, or manganese from infant formula—and exposures to pesticides and air pollution. Although studies that try to identify single risk factors in multifactorial diseases are valuable, we must not expect them to be able to provide definitive proof of the role of individual factors in complex causal networks in genetically diverse populations of people. Single risk factors act in a complicated sea of conditions that increase or decrease overall susceptibility to Parkinson's disease, Alzheimer's disease, and the Western disease cluster generally. In the final chapter, we explore the option of a more comprehensive model of health and disease within which to consider decision-making intended to prevent environmental threats to healthy aging and promote individual and community health.

Endnotes

1. Braak H, Ghebremedhim E, Rub U, Bratzke H, Del Tredici K. Stages in the development of Parkinson's disease—related pathology. Cell Tissue Res. 2004;318(1):121-134.
2. Abbott R, Ross G, Petrovitch H et al., Bowel movement frequency in late-life and incidental Lewy bodies. Mov Disord. 2007;22(11):1581-1586.
3. Haehner A, Hummel T, Hummel C, Sommer U, Junghanns S, Reichmann H. Olfactory loss may be a first sign of idiopathic Parkinson's disease. Mov Disord. 2007;22(6):839-842.
4. Abbott R, Ross G, White L, et al., Excessive daytime sleepiness and subsequent development of Parkinson disease. Neurology. 2005;65(9):1442-1446.
5. Viartis. History of Parkinson's disease. Available at: http://viartis.net/parkinsons.disease/history.htm Accessed July 4, 2008.
6. Braak H, Ghebremedhim E, Rub U, Bratzke H, Del Tredici K. Stages in the development of Parkinson's disease—related pathology. Cell Tissue Res. 2004;318(1):121-134.
7. Orimo S, Takahashi A, Uchihara T et al., Degeneration of cardiac sympathetic nerve begins in the early disease process of Parkinson's disease. Brain Pathol. 2007;17(1):24-30.
8. Shults C. Lewy bodies. Proc Natl Acad Sci USA. 2006;103(6):1661-1668.
9. Wilms H, Zecca L, Rosenstiel P, Sievers J, Deuschl G, Lucius R. Inflammation in Parkinson's diseases and other neurodegenerative diseases: cause and therapeutic implications. Curr Pharm Des 2007;13(18):1925-1928.
10. Block M, Hong J. Chronic microglial activation and progressive dopaminergic neurotoxicity. Biochem Soc Trans 2007;35(Pt 5):1127-1132.
11. McGeer P, Itagaki S, Akiyama H, McGeer E. Rate of cell death in parkinsonism indicates active neuropathologic process. Ann Neurol 1988;24(4):574-576.
12. Gerhard A, Pavese N, Hotton G, et al. In vivo imaging of microglial activation with [11C](R)-PK11195 PET in idiopathic Parkinson's disease. Neurobiol Dis. 2006;21(2):404-412.
13. Forman M, Lee V, Trojanowski J. Nosology of Parkinson's disease: looking for the way out of a quagmire. Neuron. 2005;47(4):479-82.
14. Linazasoro G. Classical Parkinson disease versus Parkinson complex – reflections against staging and in favour of heterogeneity. European Journal of Neurology. 2007;14:721-728.
15. Tanner CM, Ottman R, Goldman SM, et al. Parkinson disease in twins: an etiologic study. JAMA. 1999;281:341-346.
16. Belin A, Westerlund M. Parkinson's disease: a genetic perspective. FEBS J. 2008;275(7):1377-1383.
17. Warner T, Schapira A. Genetic and environmental factors in the cause of Parkinson's disease. Ann Neurol. 2003;53(suppl3):S16-S25.
18. Langston W, Ballard P, Tetrud J, Irwin I. Chronic Parkinsonism in humans due to a product of meperidine-analog synthesis. Science. 1983;219(4587):979-980.
19. Schober A. Classic toxin-induced animal models of Parkinson's disease: 6-OHDA and MPTP. Cell Tissue Res. 2004;318(1):215-24.
20. Hernan, Takkouche B, Caamanolsoma F, Gestel-Otero J. A meta-analysis of coffee drinking, cigarette smoking, and the risk of Parkinson's disease. Ann Neurol. 2002;52:276-284.
21. Ritz B, Ascherio A, Checkoway H, et al. Pooled analysis of tobacco use and risk of Parkinson disease. Arch Neurol. 2007;64(7):990-997.
22. Khwaja M, McCormack A, McIntosh J, DiMonte D, Quik M. Nicotine partially protects against paraquat-induced nigrostriatal damage in mice; link to alpha6beta2* nAChRs. J Neurochem. 2007;100(1):180-190.
23. Villafane G, Cesaro P, Rialland A, et al. Chronic high dose transdermal nicotine in Parkinson's disease: an open trial. Eur J Neurol Oct, 2007. Epub ahead of print.
24. Hernan, Takkouche B, Caamanolsoma F, Gestel-Otero J. A meta-analysis of coffee drinking, cigarette smoking, and the risk of Parkinson's disease. Ann Neurol. 2002;52:276-284.
25. Xu K., Bastia E. and Schwarzschild M. Therapeutic potential of adenosine A2A receptor antagonists in Parkinson's disease. Pharmacol. Ther. 2005;105, 267-310.
26. Ribeiro JA, Sebastião AM, de Mendonça A. Adenosine receptors in the nervous system: pathophysiological implications. Prog Neurobiol. 2002;68(6):377-392.
27. Popat RA, Van Den Eeden SK, Tanner CM, et al. Effect of reproductive factors and postmenopausal hormone use on the risk of Parkinson disease. Neurology. 2005;65(3):383-390.
28. Currie LJ, Harrison MB, Trugman JM, Bennett JP, Wooten GF. Postmenopausal estrogen use affects risk for Parkinson disease. Arch Neurol. 2004;61(6):886-888.
29. Bower J, Maraganore D, McDonnell S, Rocca W. Incidence and distribution of parkinsonism in Olmsted County, Minnesota 1976-1990. Neurology. 1999;52:1214-1220.
30. Elbaz A, Bower J, Maraganore D, et al. Risk tables for parkinsonism and Parkinson's disease. J Clin Epidemiol. 2002;55:25-31.
31. Van Den Eeden SK, Tanner CM, Bernstein AL, et al. Incidence of Parkinson's disease: variation by age, gender, and race/ethnicity. Am J Epidemiol. 2003;157:1015-22.
32. Koller W, Vetere-Overfield B, Gray C, et al. Environmental risk factors in Parkinson's disease. Neurology. 1990;40(8):1218-21.
33. Gorell J, Rybicki B, Johnson C, Peterson E. Occupational metal exposures and the risk of Parkinson's disease. Neuroepidemiol. 1999;18(6):303-308.
34. Brown T, Rumsby P, Capleton A, Rushton L, Levy L. Pesticides and Parkinson's disease—is there a link? Environ Health Perspect. 2006;114(2):156-64.
35. Hoppin J, Yucel F, Dosemeci M, Sandler D. Accuracy of self-reported pesticide use duration information from licensed pesticide applicators in the Agricultural Health Study. J Expo Anal Environ Epidemiol. 2002;12(5):313-318.
36. Betarbet R, Sherer TB, MacKenzie G, Garcia-Osuna M, Panov AV, Greenamyre JT. Chronic systemic pesticide exposure reproduces features of Parkinson's disease. Nat NeurosciNeurosci. 2000;3(12):1301-6.
37. Brooks A, Chadwick C, Gelbard H, et al. Paraquat elicited neurobehavioral syndrome caused by dopaminergic neuron loss. Brain Res. 1999; 823(1-2):1-10.
38. Di Monte DA The role of environmental agents in Parkinson's disease. Clin Neurosci Res 2001;1:419-426.

39. Ferraz H, Bertolucci P, Pereira J, Lima J, Andrade L. Chronic exposure to the fungicide maneb may produce symptoms and signs of CNS manganese intoxication. Neurology. 1988;38(4):550-553.
40. Meco G, Bonifati V, Vanacore N, Fabrizio E. Parkinsonism after chronic exposure to the fungicide maneb (manganese ethylene-bis-dithiocarbamate). Scand J Work Environ Health. 1994;20(4):301-305.
41. Morato G, Lemos T, Takahashi R. Acute exposure to maneb alters some behavioral functions in the mouse. Neurotoxicol Teratol. 1989;11(5):421-425.
42. Soleo L, Defazio G, Scarselli R, Zefferino R, Livrea P, Foa V. Toxicity of fungicides containing ethylene-bis-dithiocarbamate in serumless dissociated mesencephalic-striatal primary coculture. Arch Toxicol. 1996;70(10):678-682.
43. Miller D, Reinhard J, Daniels A, O'Callaghan J. Diethyldithiocarbamate potentiates the neurotoxicity of in vivo 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine and of in vitro 1-methyl-4-pehnylpyridinium. J Neurochem. 1991;57(2):541-549.
44. Thiruchelvam M, Richfield E, Baggs R, Tank A, Cory-Slechta D. The nigrostriatal dopaminergic system as a preferential target of repeated exposures to combined paraquat and maneb: implications for Parkinson's disease. J Neurosci. 2000;20(24):9207-9214.
45. Thiruchelvam M, Brockel B, Richfield E, Baggs R, Cory-Slechta D. Potentiated and preferential effects of combined paraquat and maneb on nigrostriatal dopamine systems: environmental risk factors for Parkinson's disease? Brain Res 2000;873:225-234.
46. Barlow B, Richfield E, Cory-Slechta D, Thiruchelvam M. A fetal risk factor for Parkinson's disease. Dev Neurosci. 2004;26(1):11-23.
47. Barlow B, Lee D, Cory-Slechta D, Opanashuk L. Modulation of antioxidant defense systems by the environmental pesticide maneb in dopaminergic cells. Neurotoxicology. 2005;26(1):63-75.
48. Prasad K, Winnik B, Thiruchelvam M, et al. Prolonged toxicokinetics and toxicodynamics of paraquat in mouse brain. Environ Health Perspect. 2007;115(10):1448-1453.
49. Colosio C, Fustinoni S, Birindelli S, et al. Ethylenethiourea in urine as an indicator of exposure to mancozeb in vineyard workers. Toxicol Lett 2002;134(1-2):133-140.
50. Smith J. Paraquat poisoning by skin absorption: a review. Hum Toxicol 1988;7(1):15-19.
51. Corrigan F, Wienburg C, Shore R, Daniel S, Mann D. Organochlorine insecticides in substantia nigra in Parkinson's disease. J Toxicol Environ Health A. 2000;59(4):229-234.
52. Uversky V, Li J, Fink A. Pesticides directly accelerate the rate of alpha-synuclein fibril formation: a possible factor in Parkinson's disease. FEBS Lett. 2001;500(3):105-108.
53. Goodsell D. The molecular perspective: ubiquitin and the proteosome. The Oncologist. 2003;8(3):293-294.
54. Wang X, Li S, Chou A, Bronstein J. Inhibitory effects of pesticides on proteasome activity: implication in Parkinson's disease. Neurobiol Dis. 2006;23(1):198-205.
55. Kitazawa M, Anantharam V, Kanthasamy A. Dieldrin-induced oxidative stress and neurochemical changes contribute to apoptopic cell death in dopaminergic cells. Free Radic Biol Med. 2001;31(11):1473-1485.
56. Mao H, Fang X, Floyd K, Polcz J, Zhang P, Liu B. Induction of microglia reactive oxygen species production by the organochlorinated pesticide dieldrin. Brain Res Oct 18 [Epub ahead of print], 2007.
57. Hatcher J, Richardson J, Guillot T, et al. Dieldrin exposure induces oxidative damage in the mouse nitrostriatal dopamine system. Exp Neurol. 2007;204(2):619-630.
58. Richardson J, Caudle W, Wang M, et al. Developmental exposure to the pesticide dieldrin alters the dopamine system and increases neurotoxicity in an animal model of Parkinson's disease. FASEB J. 2006;20(10):1695-1697.
59. Centers for Disease Control and Prevention. National report on human exposure to environmental chemicals. Available at: http://www.cdc.gov/exposurereport/results_12.htm Accessed Aug. 1, 2008.
60. Nasuti C, Gabbianelli R, Falcioni M, et al. Dopaminergic system modulation, behavioral changes, and oxidative stress after neonatal administration of pyrethroids. Toxicology. 2007;229(3):194-205.
61. Shantz S, Widholm J, Rice D. Effects of PCB exposure on neuropsychological function in children. Environ Health Perspect. 2003;111(3):357-376.
62. Nichols B, Hentz K, Aylward L, Hays S, Lamb J. Age-specific reference ranges for polychlorinated biphenyls (PCB) based on the NHANES 2001-2002 survey. J Toxicol Environ Health A. 2007;70(21):1873-1877.
63. Steenland K, Hein M, Cassinelli R, et al. Polychlorinated biphenyls and neurodegenerative disease mortality in an occupational cohort. Epidemiology. 2006;17(1):8-13.
64. Corrigan F, Murray L, Wyatt C, Shore R. Diorthosubstituted polychlorinated biphenyls in caudate nucleus in Parkinson's disease. Exp Neurol. 1998;150(2):339-342.
65. Seegal R, Brosch K, Shain W. Lightly chlorinated ortho-substituted PCB congeners decrease dopamine in nonhuman primate brain and in tissue culture. Toxicol Appl Pharmacol. 1990;106:136-144.
66. Seegal R, Bush B, Brosch K. Sub-chronic exposure of the adult rat to aroclor 1254 yields regionally specific changes in central dopaminergic function. Neurotoxicology. 1991;12:55-65.
67. Hennig B, Reiterer G, Majkova Z, Oesterling E, Meerarani P, Toborek M. Modification of environmental toxicity by nutrients: implications in atherosclerosis. Cardiovasc Toxicol. 2005;5:153-160.
68. Lee D, Gelein R, Opanashuk L. Heme-oxygenase-1 promotes polychlorinated biphenyl mixture aroclor 1254¬–induced oxidative stress and dopaminergic cell injury. Toxicol Sci. 2006;90(1):159-167.
69. Lee D, Opanashuk L. Polychlorinated biphenyl mixture aroclor 1254–induced oxidative stress plays a role in dopaminergic cell injury. Neurotoxicology. 2004;25(6):925-939.
70. Lee D, Gelein R, Opanashuk L. Heme-oxygenase-1 promotes polychlorinated biphenyl mixture aroclor 1254–induced oxidative stress and dopaminergic cell injury. Toxicol Sci. 2006;90(1):159-167.
71. Lee D, Opanashuk L. Polychlorinated biphenyl mixture aroclor 1254–induced oxidative stress plays a role in dopaminergic cell injury. Neurotoxicology. 2004;25(6):925-939.
72. Lee D, Gelein R, Opanashuk L. Heme-oxygenase-1 promotes polychlorinated biphenyl mixture aroclor 1254–induced oxidative stress and dopaminergic cell injury. Toxicol Sci. 2006;90(1):159-167.

73. Schipper H. Heme oxygenase expression in human central nervous system disorders. Free Radic Biol Med. 2004;37(12):1995-2011.
74. Schipper, 2004.
75. Sohn Y, Jeong Y, Kim H, et al. The brain lesion responsible for parkinsonism after carbon monoxide poisoning. Arch Neurol 2000;57(8):1214-1218.
76. Caudle W, Richardson J, Delea K, et al. Polychlorinated biphenyl–induced reduction of dopamine transporter expression as a precursor to Parkinson's disease–associated dopamine toxicity. Toxicol Sci. 2006;92(2):490-499.
77. Baker E, Smith T, Landrigan P. The neurotoxicity of industrial solvents: a review of the literature. Am J Ind Med. 1985;8(3):207-217.
78. Hageman G, van der Hoek J, van Hout M, et al. Parkinsonism, pyramidal signs, polyneuropathy, and cognitive decline after long-term occupational solvent exposure. J Neurol. 1999;246(3):198-206.
79. Tanner C. Occupational and environmental causes of parkinsonism. Occup Med. 1992;7:503-513.
80. Peters H, Levine R, Matthews C, Chapman L. Extrapyramidal and other neurologic manifestations associated with carbon disulfide fumigant exposure. Arch Neurol. 1988;45:537-540.
81. Uitti R, Snow B, Shinotoh H, et al. Parkinsonism induced by solvent abuse. Ann Neurol. 1994;35(5):616-619.
82. Guehl D, Bezard E, Dovero S, Boraud T, Bioulac B, Gross C. TCE and parkinsonism: a human and experimental observation. Eur J Neurol. 1999;6(5):609-611.
83. Reddy N, Lewis L, Gardner T, Osterling W, Eskey C, Nierenberg D. Two cases of rapid onset Parkinson's syndrome following toxic ingestion of ethylene glycol and methanol. Clin Pharmacol Ther. 2007;81(1):114-121.
84. Gash D, Rutland K, Hudson N, et al. TCE: Parkinsonism and complex 1 mitochondrial neurotoxicity. Ann Neurol. Published online Dec 21, 2007.
85. Agency for Toxic Substances and Disease Registry (ATSDR). TCE: hazard summary, created in April 1992; revised in January 2000. Atlanta: U.S. Department of Health and Human Services, Public Health Service, ATSDR, 2000.
86. Akundi R, Macho A, Munoz E, et al. 1-trichloromethyl-1,2,3,4-tetrahydro-beta-carboline-induced apoptosis in the human neuroblastoma cell line SK-N-SH. J Neurochem. 2004;91(2):263-273.
87. Riederer P, Foley P, Bringmann G, Feineis D, Bruckner R, Gerlach M. Biochemical and pharmacological characterization of 1-trichloromethyl-1,2,3,4-tetrahydro-beta-carboline: a biologically relevant neurotoxin? Eur. J. Pharmacol. 2002;442, 1–16.
88. Gorell J, Rybicki B, Johnson C, Peterson E. Occupational metal exposures and the risk of Parkinson's disease. Neuroepidemiol. 1999;18(6):303-308.
89. Rybicki B, Johnson C, Uman J, Gorell J. Parkinson's disease mortality and the industrial use of heavy metals. Mov Disord 1993:8(1):87-92.
90. Tanner C. Occupational and environmental causes of parkinsonism. Occup Med. 1992;7:503-513.
91. Tanner CM, Ottman R, Goldman SM, et al. Parkinson disease in twins: an etiologic study. JAMA. 1999;281:341–346.
92. Gaggelli E, Kozlowski H, Valensin D, Valensin G. Copper homeostasis and neurodegenerative disorders (Alzheimer's, prion, and Parkinson's diseases and amyotrophic lateral sclerosis). Chem Rev. 2006;106(6):1995-2044.
93. Erikson K, Thompson K, Aschner J, Aschner M. Manganese neurotoxicity: a focus on the neonate. Pharmacol Ther. 2007;113(2):369-377.
94. Tran T, Chowanadisai W, Crinella F, Chicz-DeMet A, Lonnerdal B. Effect of high dietary manganese intake of neonatal rats on tissue mineral accumulation, striatal dopamine levels, and neurodevelopmental status. Neurotoxicol. 2002;23(4-5):635-643.
95. Lonnerdal B. Nutritional aspects of soy formula. Acta Pediatr Suppl. 1994;402:105-108.
96. Keen C, Bell J, Lonnerdal B. The effect of age on manganese uptake and retention from milk and infant formula in rats. J Nutr. 1986;116:395-402.
97. Dorner K, Dziadzka S, Hohn A, et al. Longitudinal manganese and copper balances in young infants and preterm infants fed on breast-milk and adapted cow's milk formulas. Br J Nutr. 1989;61(3):559-572.
98. Collipp P, Chen S, Maitinsky S. Manganese in infant formulas and learning disability. Ann Nutr Metab. 1983;488-494.
99. Wasserman G, Liu X, Parvez F, et al. Water manganese exposure and children's intellectual function in Araihazar, Bangladesh. Environ Health Perspect. 2006;114(1):124-129.
100. Mergler D, Huel G, Iregren A, et al. Nervous system dysfunction among workers with long-term exposure to manganese. Environ Res. 1994;64:151-180.
101. Olanow C. Manganese-induced parkinsonism and Parkinson's disease. Ann NY Acad Sci. 2004;1012:209-23.
102. Perl D, Olanow C. The neuropathology of manganese-induced Parkinsonism. J Neuropathol Exp Neurol. 2007;66(8):675-682.
103. Santamaria A, Cushing C, Antonini J, Finley B, Mowat F. State-of-the-science review: Does manganese exposure during welding pose a neurological risk? J Toxicol Environ Health B Crit Rev. 2007;10(6):417-465.
104. Blumberg K, Walsh M. Status report concerning the use of MMT in gasoline. Intl Council on Clean Transportation. Sept, 2004. Available at: http://www.theicct.org/documents/MMT_ICCT_2004.pdf Accessed Dec 16, 2007.
105. Bolte S, Normandin L, Kennedy G, Zayed J. Human exposure to respirable manganese in outdoor and indoor air in urban and rural areas. J Toxicol Environ Health A. 2004;67(6):459-467.
106. Aschner M, Erikson K, Dorman D. Manganese dosimetry: species differences and implications for neurotoxicity. Crit Rev Toxicol. 2005;35(1):1-32.
107. Finkelstein M, Jerrett M. A study of the relationships between Parkinson's disease and markers of traffic-derived and environmental manganese air pollution in two Canadian cities. Environ Res. 2007;104(3):420-432.
108. Weiss, B. Economic implications of manganese neurotoxicity. Neurotoxicology. 2006;27, 362-368.
109. Kaur D, Andersen J. Does cellular iron dysregulation play a causative role in Parkinson's disease? Ageing Res Rev. 2004;3(3):327-343.

110. Aoki S, Okada Y, Nishimura K, et al. Normal deposition of brain iron in childhood and adolescence: MR imaging at 1.5 T. Radiology. 1989;172(2):381-385.
111. Kaur D, Andersen J. Does cellular iron dysregulation play a causative role in Parkinson's disease? Ageing Res Rev. 2004;3(3):327-343.
112. Borie C, Gasparini F, Verpillat P, et al. Association study between iron-related genes polymorphisms and Parkinson's disease. J Neurol. 2002;249(7):801-804.
113. Kaur D, Peng J, Chinta S, et al. Increased murine neonatal iron intake results in Parkinson-like neurodegeneration with age. Neurobiol Aging. 2007;28(6):907-913.
114. Dwork A. Effects of diet and development upon the uptake and distribution of cerebral iron. J Neurol Sci. 1995;134suppl:45-51.
115. Dwork A. 1995.
116. Shashiraj, Faridi M, Singh O, Rusia U. Mother's iron status, breastmilk iron and lactoferrin—are they related? Eur J Clin Nutr. 2006;60(7):903-908.
117. Lonnerdal B. Trace element transport in the mammary gland. Annu Rev Nutr. 2007;27:165-177.
118. Lonnerdal B. Nutritional aspects of soy formula. Acta Pediatr Suppl. 1994;402:105-108.
119. Rao R, Georgieff M. Iron in fetal and neonatal nutrition. Semin Fetal Neonatal Med. 2007;12(1):54-63.
120. Lozoff B, et al "Poorer developmental outcome at 10 years with 12 mg/L iron-fortified formula in infancy" PAS Meeting 2008; Abstract 5340.2.
121. Carlson E, Stead J, Neal C, Petryk A, Georgieff M. Perinatal iron deficiency results in altered developmental expression of genes mediating energy metabolism and neuronal morphogenesis in hippocampus. Hippocampus. 2007;17(8):679-691.
122. American Academy of Pediatrics. Committee on Nutrition. Iron fortification of infant formulas. Pediatrics. 1999;104(1):119-123.
123. Powers K, Smith-Weller T, Franklin G, Longstreth W, Swanson P, Checkoway H. Parkinson's disease risks associated with dietary iron, manganese, and other nutrient intakes. Neurology. 2003;60(11):1761-1766.
124. Johnson C, Gorell J, Rybicki B, Sanders K, Peterson E. Adult nutrient intake as a risk factor for Parkinson's disease. Int J Epidemiol. 1999;28(6):1102-1109.
125. Logroscino G, Marder K, Graziano J, et al. Dietary iron, animal fats, and risk of Parkinson's disease. Mov Disord. 1998;13 suppl 1: 13-16.
126. Coon S, Stark A, Peterson E, et al. Whole-body lifetime occupational lead exposure and risk of Parkinson's disease. Environ Health Perspect 2006;114(12):1872-1876.
127. Uversky V, Li J, Fink A. Pesticides directly accelerate the rate of alpha-synuclein fibril formation: a possible factor in Parkinson's disease. FEBS Lett. 2001;500(3):105-108.
128. Coon S, Stark A, Peterson E, et al. 2006.
129. Calderón-Garcidueñas L, Solt A, Henríquez-Roldán C, et al. Long-term air pollution exposure is associated with neuroinflammation, an altered innate immune response, disruption of the blood-brain barrier, ultrafine particulate deposition, and accumulation of amyloid beta-42 and alpha-synuclein in children and young adults. Toxicol Pathol. 2008;36(2):289-310.
130. Peters A, Veronesi B, Calderón-Garcidueñas L, et al. Translocation and potential neurological effects of fine and ultrafine particles a critical update. Part Fibre Toxicol. 2006;3:13. Available at http://www.particleandfibretoxicology.com/content/3/1/13 Accessed July 25, 2008.
131. LoPachin R, Gavin T, Barber D. Type-2 alkenes mediate synaptoxicity in neurodegenerative diseases. Neurotoxicology. 2008;doi:10.1016/j.neuro.2008.04.016. (Epub ahead of print]
132. Seaman V, Bennett D, Cahill T. Origin, occurrence, and source emission rate of acrolein in residential indoor air. Environ Sci Technol. 2007;41(20):6940-6946.
133. Parzefall, W. Minireview on the toxicity of dietary acrylamide. Food Chem Toxicol 2008;46(4):1360-1364.
134. Dickman M. von Economo encephalitis. Arch Neurol 2001;58(10):1696-1698.
135. Ling Z, Gayle D, Ma S, et al. In utero bacterial endotoxin exposure causes loss of tyrosine hydroxylase neurons in the postnatal rat midbrain. Mov Disord. 2002;17(1):116-24.
136. Ling Z, Zhu Y, Tong C, Snyder J, Lipton J, Carvey P. Progressive dopamine neuron loss following supra-nigral lipopolysaccharide (LPS) infusion into rats exposed to LPS prenatally. Exp Neurol 2006;199:499-512.
137. Zhu Y, Carvey P, Ling Z. Altered glutathione homeostasis in animals prenatally exposed to lipopolysaccharide. Neurochem Int. 2007;50(4):671-680.
138. Ling Z, Chang Q, Tong C, Leurgans S, Lipton J, Carvey P. Rotenone potentiates dopamine neuron loss in animals exposed to lipopolysaccharide prenatally. Exp Neurol. 2004;190(2):373-383.
139. Qin L, Wu X, Block M, et al. Systemic LPS causes chronic neuroinflammation and progressive neurodegeneration. Glia. 2007;55(5):453-462.
140. Gao X, Hu X, Qian L, et al. Formyl-methionyl-leucyl-phenylalanine-induced dopaminergic neurotoxicity via microglial activation: a mediator between peripheral infection and neurodegeneration? Environ Health Perspect 2008;116(5):593-598.
141. Hu F. Dietary pattern analysis: a new direction in nutritional epidemiology. Curr Opin Lipidol. 2002;13:3-9.
142. Gao X, Chen H, Fung T, et al. Prospective study of dietary pattern and risk of Parkinson disease. Am J Clin Nutr. 2007;86(5):1486-1494.
143. Etminan M, Gill S, Samii A. Intake of vitamin E, vitamin C, and carotenoids and the risk of Parkinson's disease: a meta-analysis. Lancet Neurol. 2005;4(6):362-365.
144. Chen H, Zhang S, Schwarzschild M, et al. Folate intake and risk of Parkinson's disease. Am J Epidemiol 2004;160(4):368-375.
145. Chen H, Zhang S, Hernan M, et al. Diet and Parkinson's disease: a potential role of dairy products in men. Ann Neurol 52(6):793-801.
146. Chen H, O'Reilly E, McCullough M, et al. Consumption of dairy products and risk of Parkinson's disease. Am J Epidemiol. 2007;165(9):998-1006.
147. Zhang S, Hernan M, Chen H, et al. Intakes of vitamins E and C, carotenoids, vitamin supplements, and PD risk. Neurology 2002;59(8):1161-1169.

148. Gao X, Chen H, Fung T, et al. Prospective study of dietary pattern and risk of Parkinson disease. Am J Clin Nutr 2007;86(5):1486-1494.
149. de Lau L, Bornebroek M, Witteman J, et al. Dietary fatty acids and the risk of Parkinson disease: the Rotterdam study. Neurology. 2005;64(12):2040-2045.
150. de Lau L, Koudstaal P, Witteman J, et al. Dietary folate, vitamin B12, and vitamin B6 and the risk of Parkinson disease. Neurology 2006;67(2):315-318.
151. Park M, Ross G, Petrovitch H. Consumption of milk and calcium in midlife and the future risk of Parkinson disease. Neurology 64(6):1047-1051.
152. Logroscino G, Marder K, Graziano J, et al. Dietary iron, animal fats, and risk of Parkinson's disease. Mov Disord 1998;13 suppl 1:13-16.
153. Powers K, Smith-Weller T, Franklin G, et al. Parkinson's disease risks associated with dietary iron, manganese, and other nutrient intakes. Neurology 2003;60(11):1761-1766.
154. Johnson C, Gorell J, Rybicki B, et al. Adult nutrient intake as a risk factor for Parkinson's disease. Int J Epidemiol 1999;28(6):1102-1109.
155. Gao X, Chen H, Choi H, Curhan G, Schwarzschild M, Ascherio A. Diet, urate, and Parkinson's disease risk in men. Am J Epidemiol 2008;167(7):831-838.
156. Chen H, O'Reilly E, McCullough M, et al. Consumption of dairy products and risk of Parkinson's disease. Am J Epidemiol. 2007;165(9):998-1006.
157. Chen H, O'Reilly E, McCullough M, et al. 2007.
158. Makino Y, Ohta S, Tachikawa O, Hirobe M. Presence of tetrahydroisoquinoline and 1-methyl-tetrahydro-isoquinoline in foods: compounds related to Parkinson's disease. Life Sci. 1988;43(4):373-378.
159. Choi H, Atkinson K, Karlson E, et al. Purine-rich foods, dairy and protein intake, and the risk of gout in men. N Engl J Med. 2004;350:1093-1103.
160. Davis J, Grandinetti A, Waslien C, Ross G, White L, Morens D. Observations on serum uric acid levels and the risk of idiopathic Parkinson's disease. Am J Epidemiol. 1996;144:480–484.
161. de Lau L, Koudstaal P, Hofman A, Breteler M. Serum uric acid levels and the risk of Parkinson disease. Ann Neurol. 2005;58:797–800.
162. Annanmaki T, Muuronen A, Murros K. Low plasma uric acid level in Parkinson's disease. Mov Disord. 2007;22(8):1133-1137.
163. Weisskopf M, O'Reilly E, Chen H, Schwarzschild M, Ascherio A. Plasma urate and risk of Parkinson's disease. Am J Epidemiol. 2007;166(5):561-567.
164. Gao X, Chen H, Choi H, Curhan G, Schwarzschild M, Ascherio A. Diet, urate, and Parkinson's disease risk in men. Am J Epidemiol 2008;167(7):831-838.
165. Bosquet M, Saint-Pierre M, Julien C, et al. Beneficial effects of dietary omega-3 polyunsaturated fatty acid on toxin-induced neuronal degeneration in an animal model of Parkinson's disease. FASEB J. 2008;22(4):1213-1225.
166. Choi J, Jang E, Park C, Kang J. Enhanced susceptibility to 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine neurotoxicity in high-fat diet–induced obesity. Free Radic Biol Med. 2005;38(6):806-816.
167. Abbott R, Ross G, White L, et al. Midlife adiposity and the future risk of Parkinson's disease. Neurology 2002;59(7):1051-1057.
168. Chen H, Zhang S, Schwarzschild M, et al. Obesity and the risk of Parkinson's disease. Am J Epidemiol 2004;159(6):547-555.
169. Hu G, Jousilahti P, Nissinen A, et al. Body mass index and the risk of Parkinson disease. Neurology 2006;67(11):1955-1959.
170. Dick F, De Palma G, Ahmadi A, et al. Environmental risk factors for Parkinson's disease and parkinsonism: the Geoparkinson study. Occup Environ Med. 2007 64(10):666-672.
171. Goldman S, Tanner C, Oakes D, et al. Head injury and Parkinson's disease risk in twins. Ann Neurol. 2006 60(1):65-72.
172. Bower J, Maraganore D, Peterson B, et al. Head trauma preceding PD: a case-control study. Neurology. 2003; 60(10):1610-1615.
173. Goldman S, Tanner C, Oakes D, et al. 2006.

Chapter 9
Healthy Aging: The Way Forward

This final chapter summarizes what we have learned and what it suggests about how to respond—individually and collectively.

In the preceding chapters we reviewed much of what is known about the underlying causes of the two most common neurodegenerative diseases, with particular attention to modifiable environmental contributors. We also identified links to a cluster of common Western diseases and environmental threats to healthy aging more generally. This final chapter summarizes what we have learned and what it suggests about how to respond—individually and collectively.

Much of what we discuss in this chapter is not new. It draws on the work of others from the fields of medicine, public health, evolutionary biology, environmental health, and ecology—and it draws on common sense. What may be new, however, is the urgency of adopting a far broader "ecological" vision of what is required to achieve healthy aging. Preventing or slowing the progression of neurodegenerative diseases is an additional reason to take actions that have already been recommended for reducing the risks of diabetes, obesity, cardiovascular disease, and some kinds of cancer. Moreover, interventions that address the structural, systemic origins of these conditions, across the human lifespan, can be designed to benefit ecosystems more generally, thereby linking healthy aging to planetary healing.

No single strategy is likely to be highly effective. Since these diseases are heterogeneous in origin, multiple interventions will be necessary to reduce their burdens. The good news is that interventions likely to be beneficial are achievable and afford multiple entry points into the cascade of events leading to degenerative disease and disability. It may take time to see results, but this should not be used as an excuse to delay.

The apple is a symbol of health (and tempation!).

In this chapter we will summarize our key findings, describe what we mean by an ecological strategy to achieve healthy aging, and conclude with policy recommendations based on such a strategy. It is true that much depends on actions and choices made by individuals. But it is also true that actions of individuals have not been sufficient

to meet health-related goals and create a healthy society. Indeed, some trends are headed in the wrong direction. Our lives are deeply embedded in larger structures that strongly influence or limit individual choices. For this reason, in order to think strategically, we must use an ecological framework or model that includes a more complete reality of the world and how we live in it.

We hope this effort will encourage others to draw their own conclusions and recommend or develop their own strategic interventions in support of healthy living throughout all stages of life. Successfully addressing the expected upsurge in age-related health conditions will require the best efforts from all of us.

Diseases involving excessive oxidative stress, inflammation, and other relevant pathologic mechanisms are not only diseases of individuals but also of communities and societies.

What Have We Learned?

In the preceding chapters we described an emerging, unifying framework for understanding two neurodegenerative diseases and related conditions. The framework has multiple levels, from sub-cellular to society as a whole, as well as multiple dimensions: biologic, social, economic, and cultural.

At the micro-level, key processes of inflammation and oxidative stress play critical roles in the development and progression of Alzheimer's disease and Parkinson's disease. These processes are also linked to diabetes, obesity, cardiovascular disease, and cancer, among others, so that we can begin to think of common mechanisms that underlie prevalent disease patterns and not just individual diseases.

These cellular and sub-cellular processes of oxidative stress and inflammation are influenced by variables at the level of the individual, community, and society: how and where we live, eat, work, play, and travel; social networks; community wellbeing; and income disparities, among others. Individuals can often make choices that will help prevent or slow the onset of neurodegenerative conditions, but community-wide features of the shared environment must also be addressed. Diseases involving excessive oxidative stress, inflammation, and other relevant pathologic mechanisms are not only diseases of individuals but also of communities and societies. And the diseases of old age do not usually begin in old age. They are influenced by many variables throughout the lifespan.

Many technologies introduced in the past 50–100 years drive inflammatory pathways and excessive oxidative stress. Trends in agriculture, food production, and nutrition—including factory farming, fast food, and processed foods—have created a pro-inflammatory nutrient profile. The material economy is infused with toxic chemicals

in products and practices that drive these and other underlying biological aspects of neurodegeneration and many other diseases. Transportation adds significantly to air pollutants that cause inflammation and oxidative stress. Socioeconomic stress and loss of social networks add to the burden. Complex interactions among these variables create the conditions from which today's patterns of disease emerge.

Many technologies introduced in the past 50–100 years drive inflammatory pathways and excessive oxidative stress.

The Ecological Health Framework

Individual behavior and environmental exposures influence health, but family-, community-, and societal-level features are also expressed in individuals, even at the cellular and sub-cellular levels. Here are some examples:

- Socioeconomic status has an effect on the risk of coronary heart disease, independent of other risk factors such as smoking or diet.[1]
- One study showed that children with asthma in low-income families have higher baseline levels of markers of inflammation than children with asthma in higher income families.[2] Another showed that, among children with asthma, poor children have more symptoms in response to traffic density than better off children in the same neighborhood.[3]
- Children who are small at birth have increased levels of markers of oxidative stress in their blood, and these changes appear to persist into later childhood.[4] Low–birth weight children are also at increased risk of developing diabetes and obesity later in life. This is generally thought to be due to fetal programming that permanently sets neuroendocrine and metabolic systems in such a way that the fetus developing in a nutrient poor environment is less able to adapt to a nutrient- and calorie-rich environment after birth. Some scientists believe that the changes associated with low birth weight also increase the risk of Alzheimer's disease later in life.[5] If this is true, then risk factors for low birth weight—for example, maternal nutrition and adverse maternal fatty acid profiles,[6] maternal age, ethnicity, smoking status, air pollution,[7] [8] and neighborhood characteristics,[9] among many others—contribute to the risk of dementia in offspring decades later.

Researchers are increasingly aware that we must look at multiple levels for explanations of diseases and disease patterns. Expanded models, sometimes called eco-social, bio-eco-social, or ecological frameworks or paradigms, are attempts to capture this awareness. These frameworks fundamentally embed health in the context of the larger community, society, and ecosystem.[10] [11] Moreover, the ecological framework not only embodies an expanded, interconnected worldview, but also suggests new approaches to research into the origins of disease and disease patterns, as well as policy interventions likely to improve health.

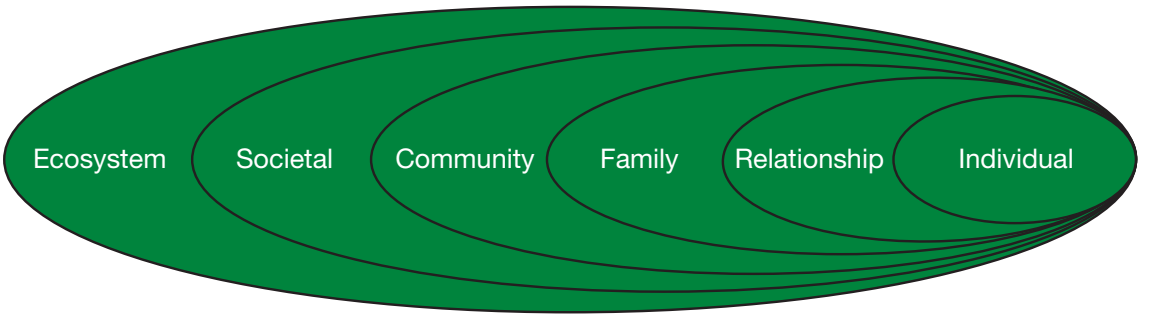

Figure 1: Ecological Model of Health/Disease

This model emphasizes the progressive nesting of individuals within families within communities and finally within ecosystems. Variables at any level can directly or indirectly influence measures of health at any level. Influences may be identifiable in individual markers such as blood pressure, atherosclerosis, and inflammatory mediators. Or they may be identifiable in neighborhood- or community-level markers such as disease patterns or socioeconomic gradient. The ecological framework implies far less distinct boundaries across levels than our medical, public health, and environmental health institutions generally acknowledge.

The causes of cases of diseases in individuals are not necessarily the same as the causes of incidence or patterns of diseases in populations. Patterns of disease are established by the distribution of risk factors throughout a population, but an individual's risk of a disease is influenced by individual susceptibility and the specific aggregation of risk factors in that person. For example, in some people with Parkinson's disease, pesticides are likely to have played a larger role than in others. Similarly, in some people with Alzheimer's disease, air pollution or diet is likely to have played a larger role than in others. Consequently, the effect of population-wide interventions on specific individuals will remain uncertain.

Nevertheless, even modest reductions in risk factors at the population-wide level can have major public health benefits. This is particularly true when a large fraction of the population is exposed to the hazard. Then, even a small reduction in disease risk can

translate into a large number of cases avoided. For example, in 2002 a large controlled study of health effects associated with hormone replacement therapy concluded that treated women had a 26% higher risk of developing breast cancer than controls.[12] (The hazard ratio was 1.26; 95 percent confidence interval 1.00-1.59.)[a] When that information was publicized, prescriptions for hormone replacement therapy plummeted nationwide. Breast cancer surveillance data show a drop in post-menopausal breast cancer incidence beginning soon thereafter, with an estimate of approximately 14,000 fewer cases in 2003 compared to 2002.[13] For each individual woman, the excess risk of breast cancer from the therapy was estimated to be small, but at a population wide level, the impact quite large. Even though some uncertainty persists, most commentators believe that the decline in hormone replacement therapy is responsible for the drop in breast cancer incidence in post-menopausal women.

Even modest reductions in risk factors at the population-wide level can have major public health benefits.

Keeping this experience in mind helps when thinking about potential public health benefits of interventions intended to address diseases of aging addressed in earlier chapters. For example, as discussed in chapter 8, although we will never have data from a controlled trial, considerable evidence shows that it is highly likely that pesticide exposures increase the risk of Parkinson's disease. Since a large portion of the general population is exposed to pesticides, even if the increased risk conferred by them were modest, a sharp reduction in exposures would likely result in a decrease in Parkinson's disease within the population.[b]

Similarly, we predict that population-wide shifts toward the Mediterranean diet would significantly decrease the incidence of diabetes, obesity, cardiovascular disease, and Alzheimer's disease. That does not mean that everyone eating a Mediterranean diet will be spared from these conditions. In some people, other risk factors may be determinative, regardless of diet. But from a public health perspective, that kind of dietary modification is highly likely to be beneficial and can easily be supported by the evidence.

Finally, the ecological framework also reminds us that, in some individuals, risk factors of modest size in populations can

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[a] *The report also noted increases in the risk of heart disease, stroke, and blood clots.*

[b] *Changes in exposure patterns will depend on the nature of interventions. Fundamental shifts in agricultural practices will be necessary to protect agricultural workers and communities who are among the most highly exposed groups. Shifts in pest control practices in housing will be necessary to protect tenants who often have little control over pesticide use. Population-wide decreases could shift high exposure groups into moderate level exposures and moderate exposure groups into low level exposures. Reductions in pesticide exposures are also likely to reduce a number of other diseases and disabilities linked to pesticides not discussed herein.*

be much more significant when they occur together with others. For example, poverty, dietary iron deficiency, and lead exposure are independent risk factors for cognitive impairment in children. When they occur together, they act as effect modifiers, meaning that the presence of one or more increases the impacts of another. The consequences of lead exposure are worsened by iron deficiency because lead uptake from the intestine and lead deposition in the brain increase.[14 15] Moreover, a child living in poverty, exposed to lead, and eating a diet deficient in iron is not only unlikely to achieve full neurodevelopmental potential but also may be at increased risk of earlier and more severe cognitive decline later in life.

The ecological framework reminds us that, in some individuals, risk factors of modest size in populations can be much more significant when they occur together with others.

Applying the Ecological Health Model to Aging and Neurodegenerative Disease

Despite remaining uncertainties about which are causes and which are consequences of disease progression, considerable evidence shows that the mechanisms of inflammation and oxidative stress are intimately involved in the cascade of events leading to the onset of Alzheimer's and Parkinson's diseases. An ecological perspective calls our attention to how factors at many levels (individual, family, community, societal, ecosystem) can pathologically upregulate oxidative stress and inflammation and thereby influence risk in individuals and patterns of disease in populations. We can also see why the age-adjusted incidence and prevalence of Alzheimer's disease may vary from one society to another, depending on the distribution of risk factors within them.[c]

Attempts to diagram such a framework, however, often end up with an "arrow salad" in which it appears that everything causes everything else. Such complex interconnections make it difficult to quantify with certainty the extent to which a single variable contributes to a particular outcome.

With conditions like diabetes, cardiovascular disease, cancer, and in all likelihood, Alzheimer's disease and Parkinson's disease,

[c] *It may or may not be true that the incidence and prevalence of Parkinson's disease varies similarly but data are not sufficient to draw any conclusions.*

FOOD *for* THOUGHT

Farm-To-School, Farm-To-Hospital Food Programs

The nature of the American diet has changed dramatically over the past 50–100 years. Most of today's food production and distribution system depends heavily on large inputs of fuel, chemicals, and fertilizer. Trends in chronic disease and ecosystem health are significantly linked to that system through nutritional deficits and imbalances; chemical contamination of food, water, soil, and air; loss of biodiversity and habitat; and hardship in rural communities.

In recent years, efforts to strengthen supply and demand for nutritious, locally produced food have found rapidly growing opportunities in farm-to-school and farm-to-hospital programs. Many schools and hospitals are now featuring fresh farm foods, often certified organic or produced in ways more ecologically sustainable than typical in high-input, industrialized agricultural systems. These programs have several objectives and address multiple problems.

These programs offer reliable, stable markets for small farmers, thereby helping the local economy.

Kaiser-Permanente now hosts more than 20 farmers' markets at its healthcare facilities in several states

Farm-to-school programs improve student nutrition and can help educate students about the links between nutrition and health. This is increasingly urgent given current trends in obesity, diabetes, heart disease, Alzheimer's disease, and cancer, each of which is linked in varying degrees with lifelong eating habits that are established early. In addition, students can learn about the connections between food production methods and the health of ecosystems.

Farm-to-hospital programs provide nutritious food to patients, staff, and visitors. More than 120 healthcare facilities in 21 states have signed "The Healthy Food in Health Care Pledge," committing to increase local purchasing and offerings of fresh fruit and vegetables and meat and milk produced without the use of hormones or antibiotics.

In some cases, hospitals provide space for local farmers' markets, improving access of neighborhood residents to locally produced, nutritious food. For example, Kaiser-Permanente

In recent years, efforts to strengthen supply and demand for nutritious, locally produced food have found rapidly growing opportunities in farm-to-school and farm-to-hospital programs.

now hosts more than 20 farmers' markets at its healthcare facilities in several states. These may be the only readily available source of fresh, nutritious food in neighborhoods with no nearby supermarkets. Programs that bring more nutritious food into hospitals are also a highly visible signal that the medical sector takes seriously the connections between health and nutrition. Finally, these programs offer reliable, stable markets for small farmers, thereby helping the local economy.

These programs do even more. By emphasizing the connections among nutrition, human health, and the health of the land, they add to the incentives and pressures for more widespread, fundamental, and sustainable changes in food production, marketing, and distribution.

Resources:

The National Farm to School Program is a collaborative program of the Center for Food and Justice at Occidental College and Community Food Security Coalition. For more information, see http://www.farmtoschool.org/aboutus.php.

Farm-to-hospital programs are featured in the work of Health Care Without Harm, an international campaign working to transform the health care sector so that it is no longer a source of harm to people or the environment. For more information, see http://www.noharm.org.

we need to rethink what we actually mean when we say that some particular variable "causes" the disease to occur. In multi-factorial diseases single factors are rarely fully explanatory, and proving causation can be difficult indeed. Yet, in order to prevent the onset or progression of these illnesses, individuals and public policy decision-makers often must act without absolute proof of the role of each variable. Sixty years of "tobacco science," during which tobacco company scientists and executives argued that there was no proof that cigarettes caused lung cancer, should have taught us that to wait for absolute proof is to wait too long.

The good news is that the multiplicity of contributing factors provides multiple entry points for beneficial interventions. The ecological framework shows that many risk factors can be addressed at multiple levels. For example, both increased exercise and decreased caloric intake will help to reduce obesity. These can be addressed through individual behavioral change and through action at the community level to ensure that sidewalks, bicycle paths, parks, safe neighborhoods, and nutritious food are accessible and available to all. In complex systems, although we can never predict all of their results, interventions can be guided by principles, available evidence, and monitoring for consequences—unintended as well as intended.

Knowing about effect modifiers is also helpful for guiding the design of policy interventions. For example, a recent cross-sectional study of 1,375 men and women reports that narrowing of the carotid artery because of atherosclerosis is inversely associated with cognitive function, but only in those participants of low socioeconomic status.[16] In other words, low socioeconomic status is an effect modifier of carotid artery narrowing, increasing its detrimental impact on cognitive ability. One potential explanation for this finding is lack of brain reserve or plasticity in individuals of low socioeconomic status. Whatever the biologic underpinnings, the study suggests that efforts that successfully decrease risks of atherosclerosis will be especially helpful in people of lower socioeconomic status. But it also means that cognitive function can be preserved by decreasing the socioeconomic gradient. We do not need to choose between the two and may actually identify interventions that address both.

We should not hesitate to identify multiple opportunities to reduce the drivers of oxidative stress and inflammation—including diabetes, obesity, chemical exposures, and socioeconomic disparities—at multiple levels, in individuals and the population as a whole.

No risk factor should be exempt. We can confidently predict that, when successful, these efforts will have beneficial effects on multiple diseases and disabilities.

Creating More Stable Conditions for Health

Borrowing from the field of ecology, it may be useful to think of the systems in which we live as basins shaped by certain conditions that tend to be self-reinforcing. Some sets of conditions—represented in Figure 2 as Basin A—are likely to promote health, while others - Basin B - are not. A person or group's location within a given set of system conditions will be a strong determinant of how precarious their circumstances are, and that can change over time. The conditions and residents of healthy Basin A provide ongoing opportunities for primary and some secondary disease prevention. In Basin B, the emphasis must be on early detection and treatment of disease, although there will be some opportunities for secondary prevention.[d]

The system conditions that shape each basin may change. For example, changes in weather patterns, crop failures, armed conflict, economic instability, or epidemic disease can cause abrupt changes in system conditions, making system inhabitants suddenly vulnerable to disease or injury from which they were previously

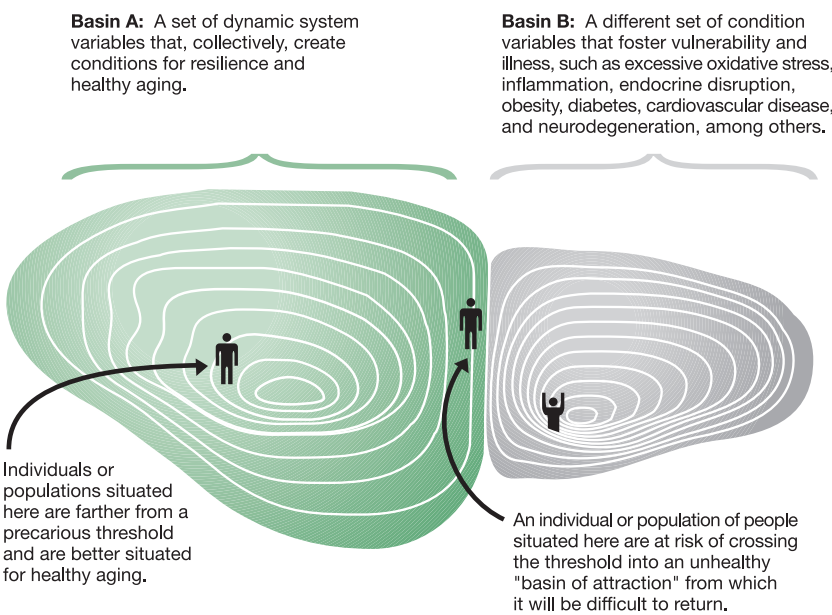


Figure 2:

Graphic depictions of dynamic systems comprised of collections of ecosocial variables in which individuals and communities live. In the field of ecology these are called basins of attraction and the bottoms of the bowls are the attractors.[17] See text for further explanation.

[d] *By primary prevention, we mean prevention of the onset of a disease process. Secondary prevention refers to preventing complications from a disease process that is already initiated.*

buffered (Basin A becomes small and shallow). System conditions can also change more slowly, and as they do, shifts in health and wellbeing are likely, with the most vulnerable being the first to experience consequences of the change.

Two general approaches can maximize the likelihood that individuals and communities will remain in Basin A: 1) move them away from the precarious Basin B threshold or 2) change the shape of Basin A so that it is deeper and wider and fewer people find themselves near the Basin B threshold.

Medical practice tends to focus on moving individuals away from the threshold in basin A and responding once they have crossed into Basin B. Public health practice adds attempts to change the shape and size of Basin A so that fewer people find themselves near the threshold and struggling in Basin B. A combination of individual and system-wide approaches can build resilience, making the unhealthy sink less available and maximizing opportunities for remaining in the health-promoting system. An ecological approach addresses both individual actions and societal conditions.

Human existence requires living within the regenerative capacity of the biosphere.

A large number of changes that have occurred in the U.S. and much of the industrially developed world over the past 50–100 years have sufficiently altered conditions so that more people are living precariously near or beyond threshold conditions that collectively foster many of today's prominent diseases, including those discussed in this report. Our task, then, is not only to respond to the medical and social needs of people in or headed toward basin B, but to try to optimize system conditions so that fewer people find themselves at risk.

Three further premises must guide our decisions:

- Human existence requires living within the regenerative capacity of the biosphere. Objective data overwhelming support the conclusion that human activity on the planet already exceeds that capacity and has for some time.[18]
- Organizing human existence on earth in ways that are sustainable and just and that acknowledge and respect universal human rights is both desirable and possible. In a world of intricate interdependencies, the quality of life of all people must be considered when making decisions. For example, agricultural policies that do not take into account food access and the economic security of farmers in developing countries are neither sustainable nor just. A large body of literature shows that the position of an individual,

Health, Wealth, and Poverty

Nancy Adler from the University of California, San Francisco and many of her colleagues have gathered a wealth of publicly available information describing the medical and public health implications of the socioeconomic ladder and its steepness.[21] Many health disparities are directly related to conditions of life at various positions on the ladder. People at the bottom are often poorly educated, unemployed or in low-wage jobs, have little savings and other resources to rely on, and live in substandard conditions. These lives are stressful. Stress is caused both by adverse circumstances and limited ability to alter them because of lack of control and limited resources. People living lower on the socioeconomic ladder are at higher risk of heart disease, diabetes, obesity, hypertension, and most kinds of cancer. They also tend to have higher levels of markers of inflammation, which is likely to help explain these higher risks.[22 23] For a variety of reasons, people lower on the socioeconomic ladder are also likely to have less education, which increases the risk of Alzheimer's disease/dementia and its consequences. In other words, the diseases of the Western disease cluster are over-represented in people lower on the ladder.

Disparities in health are not confined to people living in poverty. They are present at every level of the socioeconomic ladder.

In the World Values Survey, including forty countries, Americans were much more likely than Europeans (71 percent v. 40 percent) to agree with the statement that the poor could escape poverty if they worked hard enough.[24 25] This may reflect the strong cultural individualism dominant in the U.S. since its origins. It may mean that we generally have little interest in attacking the root causes of poverty with public resources. It may also signal that we have limited interest in using public resources to close the gap at any level. But, the disparities in health are not confined to people living in poverty. They are present at every level of the socioeconomic ladder. Thus, as the gradient becomes steeper and the ladder longer, the disease burden attributable to income inequalities will continue to grow. A decrease in social capital in large groups of people who are marginalized is likely to accompany increasing inequalities. Less social cohesion coupled with the demographic shifts outlined in chapter 1 will almost certainly be a recipe for less healthy aging. We are ill prepared to deal with the consequences of these trends, and yet objective data make clear what lies ahead.

Two kinds of policies are required to eliminate socioeconomic disparities and their health consequences.[26] The first is policies that directly reduce disparities and make it easier for everyone to move up the ladder. Examples include access to high quality education, starting in early childhood; increasing the number of households with adequate income through a variety of means including tax policies; and improving access to opportunities for new or enhanced job skills. A second kind of policy blunts the consequences, including health risks, associated with position on the socioeconomic ladder. This includes, for example, ensuring universal access to health care, ensuring affordable, safe, and healthy housing and neighborhoods; limiting workplace exposures to physical hazards, chemicals, and psychosocial stress, providing for more worker- and family-friendly work environments; providing leave time for family illnesses and emergencies; and ensuring that all individuals and neighborhoods have access to nutritious food.

family, or neighborhood on the socioeconomic ladder is consistently a strong predictor of health. (See "Health, Wealth, and Poverty.) Illnesses and environmental degradation related to poverty and socioeconomic disparities have consequences for society at large, nationally and internationally.

- Disease prevention should be raised to a much higher priority than is reflected in current policies that overwhelmingly direct resources toward early diagnosis and treatment. Primary prevention can have a large return on investment[19] and can reduce the environmental and public health impacts of the healthcare industry itself.[20]

These premises are interdependent and they are not really optional if long term human survival with lives of quality is a goal. Vast and growing numbers of the world's population are entering a period of unprecedented challenges to health, security, and survival. No sector of society or institution can ignore these issues as they plan future activities

Policy Interventions

The following are basic areas we believe must be addressed at societal levels. Important, highly relevant recommendations at a personal and family level follow in *Approaches to Healthy Living*.

Rather than be prescriptive, we provide a few examples. We hope that others working in these sectors and at all ecosystem levels will participate in co-creating a new framework for health.

1) Nutrition:

Healthy nutrition is essential, beginning with fetal development and continuing through infancy, childhood, adolescence, and all stages of adulthood into the elder years. Lifelong nutrition is strongly connected with health in later years. Our *Approaches to Healthy Living* spell out many dietary recommendations for individuals. What follows are additional important considerations. Given all we know about the origins of the diseases of aging, it is appropriate to focus many of our recommendations on the beginning of life.

Community, Workplace

- Communities should ensure that all residents have access to healthy foods and not live in "food deserts" where they can only

buy processed and packaged foods. Recently, a community in Los Angeles, CA banned additional fast food restaurants and is encouraging healthier alternatives.[27]

- Maternal and child health policies and programs, starting with prenatal education and through programs like Women, Infants and Children (WIC) and food stamps, should prioritize optimum nutrition. Hospital personnel and healthcare providers should be educated about the benefits of exclusive breast feeding for the first six months of life and institute comprehensive supportive programs. No hospital should send new parents home with gift packs containing infant formula. That practice, no matter how well-meaning, is associated with decreased length of breast feeding.[28] Workplaces could be strongly encouraged to make accommodations for mothers to breast feed their infants after returning to work.
- Communities should consider requiring fast-food restaurants to prominently display caloric content of menu items. A recent study shows that this practice results in fewer purchased calories.[29]
- Various school-based obesity intervention programs have been tried.[30] No one program design has proven best and to some extent, optimal programs will depend on specific demographics of the population, school setting, and other local details. For that reason, school boards and officials should undertake a review of available data and adopt programs best suited to their circumstances. School vending machines should not sell unhealthy processed, high-calorie, snack food.
- Healthy food as outlined in the *Approaches to Healthy Living* should be served at hospitals, nursing homes, and other places where the aged and other vulnerable groups spend time.
- Community gardens, farmers markets, food coops, community supported agriculture (CSA) organizations, and "buy local" campaigns help promote local, diversified, sustainable, and nutritious food production and foster community relationships.

National

- Farm policies should not subsidize those foods or agricultural practices that contribute to obesity, diabetes, cardiovascular disease, and cognitive decline. Rather, agricultural subsidies should be directed toward programs and practices that provide sufficient nutritious, sustainably produced food and restore ecosystems that have been degraded by agricultural activities.

- Establish and support a research agenda intended to identify climate-friendly agriculture(s) that use less energy, require fewer inputs, and reduce water use. The specifics of appropriate agricultural models are highly dependent on place. However, certain underlying principles can be established and serve as guides.[31]

International

- Trade policies should foster sustainable food production, worker protection, and replenishment of natural resources.
- Technology sharing between donor and developing states with a focus on sustainable practices should be emphasized.

2) Toxicants:

Chemical trespass, whereby people are exposed to hazardous substances unknowingly or against their will, beginning in the womb and continuing throughout life, should not be tolerated. We should make every effort to prevent exposures, replace toxicants with safer alternatives, and minimize exposures especially to the most vulnerable populations.

People are exposed to hazardous substances unknowingly or against their will, beginning in the womb and continuing throughout life.

Community, Workplace:

- Adopt community-wide policies, including in schools, other public buildings, senior centers, nursing homes and other facilities that support or care for the elderly, that discourage or prohibit unnecessary use of pesticides, including for cosmetic purposes; promote Integrated Pest Management.
- Assess, monitor, and remediate hazardous waste sites; inventory and publicize sources of hazardous emissions.
- Promote lead paint testing and abatement in residences; promote childhood lead screening.
- Workplaces should commit to providing appropriate information and protecting workers by eliminating hazardous materials from use when safer alternatives exist; fully protect workers when hazardous exposures may occur.
- Develop and promote "green" jobs and industries.
- Commit to increasing community waste reduction and recycling efforts; set goals, monitor, adjust strategies.
- Promote public transportation to decrease fuel consumption and air pollution.

National:

- Pre-market safety evaluation of pesticides should require assessment of impacts on the developing nervous system.
- Non-pesticidal industrial chemicals are currently regulated under the Toxic Substances Control Act (TSCA). For more than 25 years TSCA has failed to protect people, wildlife, and the general environment from exposures to hazardous chemicals.[32] In fact, TSCA has helped to create and maintain data, safety, and technology gaps, rewarding ignorance and failing to provide incentives for development of safer materials.[33] National chemical policy reform is essential and elements of reform should include[34]:
  - Require safer substitutes and solutions. Seek to eliminate the use and emissions of hazardous chemicals by altering production processes, substituting safer chemicals, redesigning products and systems, rewarding innovation and re-examining product function.
  - Phase out persistent, bioaccumulative, or highly toxic chemicals.
  - Give the public and workers the full right-to-know and participate: Provide meaningful involvement for the public and workers in decisions on chemicals. Disclose chemicals and materials, list quantities of chemicals produced, used, released, and exported, and provide public/worker access to chemical hazard, use and exposure information.
  - Act on early warnings: Prevent harm from new or existing chemicals when credible evidence of harm exists, even when some uncertainty remains regarding the exact nature and magnitude of the harm.
  - Require comprehensive safety data for all chemicals: For a chemical to remain on or be placed on the market manufacturers must provide publicly available safety information about that chemical. This is the principle of "No Data, No Market."
  - Take immediate action to protect communities and workers: When communities and workers are exposed to levels of chemicals that pose a health hazard, immediate action is necessary to eliminate these exposures. No population should be disproportionately exposed to hazardous chemicals.
- Prioritize clean, sustainable energy production from renewable sources; promote energy conservation

International:

- Support the United Nations Environment Program's Strategic Approach to International Chemicals Management (SAICM). SAICM was developed by a multi-stakeholder committee and supports the achievement of the goal agreed at the 2002 Johannesburg World Summit on Sustainable Development of ensuring that, by 2020, chemicals are produced and used in ways that minimize significant adverse impacts on the environment and human health.[35]
- Support efforts to sharply curtail green house gas emissions, mitigate climate change, and reduce hazards associated with energy production.

3) Exercise, Physical Activity

Regular exercise and physical activity is essential to good health and should be encouraged and supported at all ages.

Community:

- City programs, planning, and development should reflect an understanding of the health-promoting, disease-preventing qualities of regular exercise and provide safe recreational areas for all ages and neighborhoods. Development and maintenance of green spaces and parks based on design principles that have been demonstrated to work will increase their use for exercise.[36]
- Physical education should be promoted and protected in school curricula. Exercise should be part of regular routines at facilities that support and care for elders. Nursing homes, assisted living, and other care facilities should incorporate outdoor exercise areas into their designs.
- City planners should explore options for discouraging driving in towns and cities; build bike paths and commit to sidewalk maintenance, repair, and lighting. Public transportation systems should complement and interface with pedestrian walkways and bike paths.
- Employers should be encouraged to promote walking and cycling to work and to provide opportunities for employees to walk and exercise during breaks.

National:

- Search for and eliminate transportation subsidy programs that might create disincentives for physical activity and exercise.

4) Cross-cutting Solutions

Some policy interventions are cross-cutting, addressing multiple risk factors simultaneously. For example:

- Encouraging more localized, diversified, and sustainable food production rather than factory farming would enhance nutrition, strengthen local economies, reduce reliance on pesticides, and minimize the use of fossil fuels for long distance transport. This would reduce air and water pollution as well as greenhouse gas emissions.
- Transitioning to clean, renewable energy and reducing fossil fuel consumption in general would drastically reduce air pollution and its multiple adverse health impacts, while undercutting a host of harmful chemical exposures related to production, transport, and use of fossil fuels. Prioritizing the development of energy-efficient mass transit systems that interface with bike paths and sidewalks would save energy while minimizing air pollution and combating obesity.
- Reducing use of toxic substances in the home, workplace, and community through "safer substitute" programs and green product design can reduce exposures that contribute to neurodegeneration and many other chronic diseases, reduce ecosystem and wildlife contamination, and create new jobs.
- Reducing socioeconomic disparities and making certain that all people have access to affordable health care, as a right and a matter of decency, will reduce the general chronic disease burden and help to alleviate its consequences for individuals and society.

These recommendations are only examples of interventions that would help to address the oncoming wave of age-related chronic disease. They obviously cut a wide swath through many features of contemporary society and sound like part of a more comprehensive environmental public health agenda—yet they are exactly what's needed. Enough evidence is in to make that case.

We do not underestimate the breadth of these ideas. The ways that we are growing our food, what we are eating, the toxic chemicals we are exposed to, the way that we are organizing and building our houses and communities, moving around, working, and spending leisure time are directly related to the chronic disease burden that we face—individually and collectively. This suggests many opportunities for interventions which alone may only be piecemeal, but collectively add up to real change.

Resistance is certain. Interest groups benefiting from the status quo will lay blame elsewhere and conflate scientific uncertainties with "junk science."[37] [38] They will demand absolute proof before acceding to demands for preventive action. The proposed ban on additional fast food restaurants in a Los Angeles community drew criticism for intervening in personal choice, singling out one kind of restaurant, not going far enough, and failing to address other causes of obesity.[39] Yes indeed, obesity is a result of many variables, and we can only hope that this effort will be combined with others to address the problem further in this burdened community. But they deserve credit for taking this on as an urgent public health concern requiring more than handing out pamphlets about healthy eating habits.

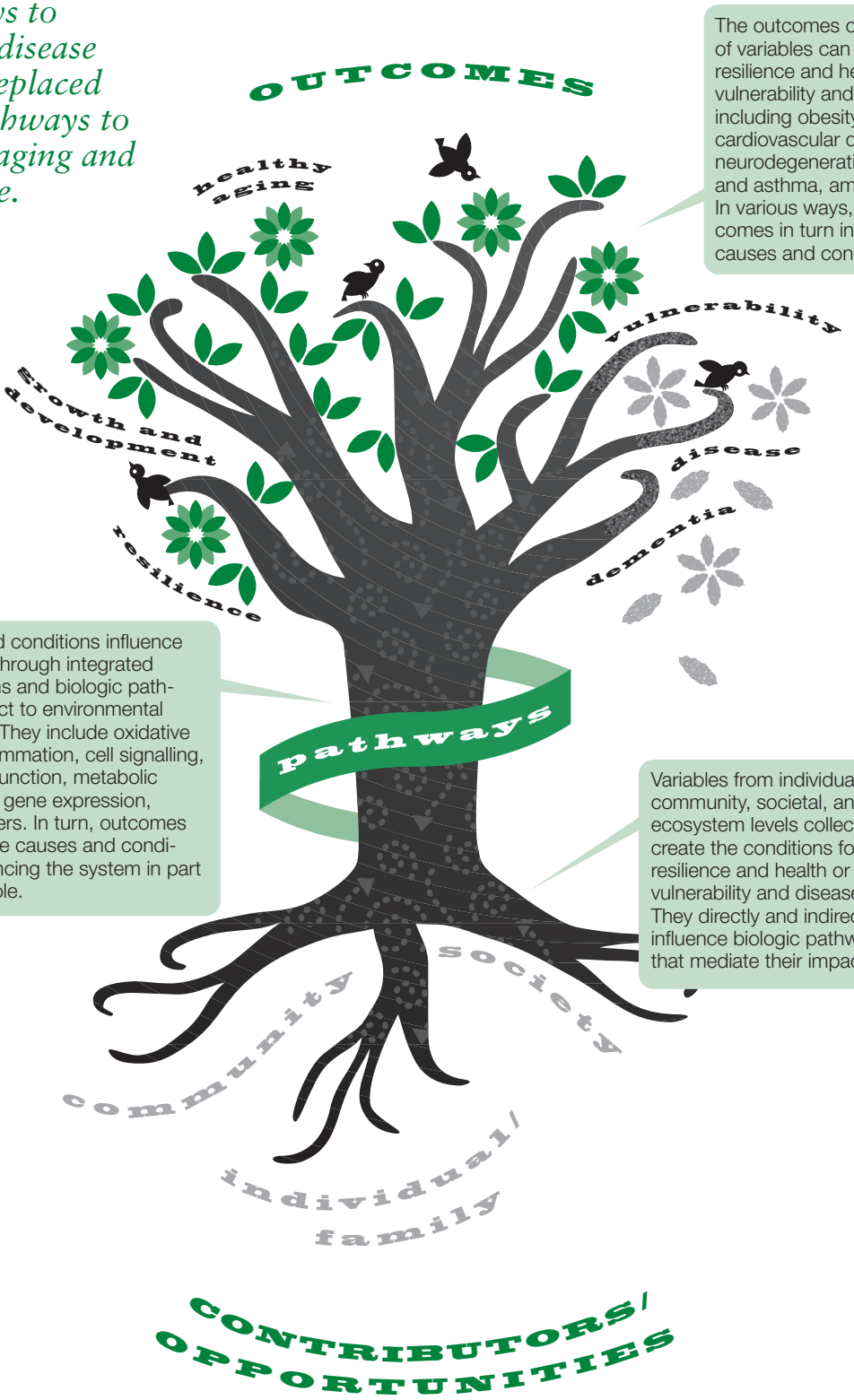
Our synthesis concludes that primary prevention ... is a real possibility and now is the time to get on with it—from many directions.

Many medical and public health planners are putting their hopes in silver bullet pharmaceutical interventions to slow or treat diseases of aging like Alzheimer's disease. Our synthesis concludes that primary prevention of much of this disease burden is a real possibility and now is the time to get on with it—from many directions.

Myriad factors contribute to resilience and health or alternatively, to vulnerability and disease. Excessive and prolonged levels of oxidative stress, inflammation, endocrine disruption, mutagenesis, and other pathological processes from exposures to toxic chemicals, social stress, and nutritional imbalances can be integrated into the lifeblood flowing though individuals and communities, or it can be otherwise. Pathways to chronic disease can be replaced with pathways to healthy aging and resilience (see figure).

The public health, economic, social, environmental, and security consequences of the choices that we make are increasingly clear. The health of this and future generations depends on acting wisely—with foresight and humility. It also depends on our summoning the political will and power to create the change that needs to happen if we are to pass on to future generations a world in which they can live lives of quality.

Pathways to chronic disease can be replaced with pathways to healthy aging and resilience.



The outcomes of this mix of variables can vary from resilience and health to vulnerability and disease–including obesity, diabetes, cardiovascular disease, neurodegeneration, cancer, and asthma, among others. In various ways, these outcomes in turn influence root causes and conditions.

Causes and conditions influence outcomes through integrated mechanisms and biologic pathways subject to environmental influences. They include oxidative stress, inflammation, cell signalling, endocrine function, metabolic status, and gene expression, among others. In turn, outcomes can become causes and conditions influencing the system in part or as a whole.

Variables from individual, community, societal, and ecosystem levels collectively create the conditions for resilience and health or vulnerability and disease. They directly and indirectly influence biologic pathways that mediate their impacts.

Endnotes

1. Adler N, Singh-Manoux A, Schwartz J, Stewart J, Matthews K, Marmot M. Social status and health: a comparison of British civil servants in Whitehall-II with European- and African-Americans in CARDIA. Soc Sci Med. 2008:1034-1045.
2. Chen E, Hanson M, Paterson L, Griffin M, Walker H, Miller G. Socioeconomic status and inflammatory processes in childhood asthma: the role of psychological stress. J Allergy Clin Immunol. 2006;117(5):1014-1020.
3. Meng Y, Wilhelm M, Rull R, English P, Nathan S, Ritz B. Are frequent asthma symptoms among low-income individuals related to heavy traffic near homes, vulnerabilities, or both? Ann Epidemiol. 2008;18(5):343-350.
4. Franco M, Kawamoto E, Gorjao, et al. Biomarkers of oxidative stress and antioxidant status in children born small for gestational age: evidence of lipid peroxidation. Pediatr Res. 2007;62(2):204-208.
5. Ross M, Desai M, Khorram O, McKnight R, Lane R, Torday J. Gestational programming of offspring obesity: a potential contributor to Alzheimer's disease. Curr Alzheimer Res. 2007;4(2):213-217.
6. Van Eijsden M, Hornstra G, van der Wal M, et al. Maternal n-3, n-6, and trans fatty acid profile early in pregnancy and term birth weight: a prospective cohort study. Am J Clin Nutri. 2008;87(4):887-895.
7. Brauer M, Lencar C, Tamburic L, et al. A cohort study of traffic-related air pollution impacts on birth outcomes. Environ Health Perspect. 2008;116(5):68-686.
8. Ritz B, Wilhelm M. Ambient air pollution and adverse birth outcomes: methodologic issues in an emerging field. Basic Lin Pharmacol Toxicol. 2008;102(2):182-190.
9. Vinikoor L, Kaufman J, MacLehose R, Laraia B. Effects of racial density and income incongruity on pregnancy outcomes in less segregated communities. Soc Sci Med. 2008;66(2):255-259.
10. Krieger N. Epidemiology and the web of causation: has anyone seen the spider? Soc Sci Med. 1994;39:887–903.
11. Susser E. Eco-Epidemiology: Thinking Outside the Black Box. Epidemiology. 2004;15(5):519-520.
12. Writing group for the Women's Health Initiative investigators. Risks and benefits of estrogen plus progestin in healthy postmenopausal women. JAMA;2002;288:321-333.
13. Ravdin P, Cronin K, Howlader N, et al. The decrease in breast-cancer incidence in 2003 in the United States. N Engl J Med; 2007;356(16):1670-1674.
14. Hubbs-Tait L, Nation J, Krebs N, Bellinger D. Neurotoxicants, micronutrients. and social environments. Individual and combined effects on children's development. Psychological Science in the Public Interest; 2005;6(3):57-121.
15. Weiss B, Bellinger D. Social ecology of children's vulnerability to environmental pollutants. Environ Health Perspect. 2006;114(10):1479-1485.
16. Singh-Manoux A, Britton A, Kivimaki M, Gueguen A, Halcox J, Marmot M. Socioeconomic status moderates the association between carotid intima-media thickness and cognition in midlife: evidence from the Whitehall II study. Atherosclerosis. 2008;541-548.
17. Walker B, Holling C, Carpenter S, Kinzig A. Resilience, adaptability and transformability in social–ecological systems. Ecology and Society. 2004;9(2): 5. Available at http://www.ecologyandsociety.org/vol9/iss2/art5 Accessed June 18, 2008.
18. Wackernagel M, Schulz N, Deumling D, et al. Tracking the ecological overshoot of the human economy. Proc Natl Acad Sci USA. 2002;99(14):9266-9271.
19. Trust for America's Health. Prevention for a Healthier America: Investments in disease prevention yield significant savings, stronger communities. Available at http://healthyamericans.org/reports/prevention08/ Accessed Aug. 1, 2008.
20. See Health Care Without Harm. www.noharm.org Accessed Aug. 9, 2008.
21. MacArthur network on SES and health. Available at http://www.macses.ucsf.edu/Default.htm Accessed Aug. 9, 2008.
22. Alley D, Seeman T, Ki Kim J, et al. Socioeconomic status and C-reactive protein levels in the US population: NHANES IV. Brain Behav Immun. 2006;20(5):498-504.
23. Nazmi A, Victora C. Socioeconomic and racial/ethnic differentials of C-reactive protein levels: a systematic review of population-based studies. BMC Public Health. 2007;7(147):212. Available at: http://www.biomedcentral.com/1471-2458/7/212 Accessed Aug. 9, 2008.
24. Gudrais E. Unequal America. Harvard Magazine. July/Aug 2008:22-29. Available at: http://harvardmagazine.com/2008/07/unequal-america.html Accessed Aug. 9, 2008.
25. World Values Survey. Available at: http://www.worldvaluessurvey.org/ Accessed Aug. 9, 2008.
26. Adler N, Stewart J, et al. Reaching for a Healthier Life: Facts on Socioeconomic Status and Health in the U.S. The John D. and Catherine T. Macarthur Foundation Research Network on Socioeconomic Status and Health. 2007. Available at: http://www.macses.ucsf.edu/News/Reaching%20for%20a%20Healthier%20Life.pdf Accessed Aug. 9, 2008.
27. Steinhauer J. Fast-food curb meets with ambivalence in South Los Angeles. New York Times. Aug. 9, 2008.
28. Kaplan D, Graff K. Marketing breastfeeding-reversing corporate influence on infant feeding practices. J Urban Health. 2008;85(4):486-504.
29. Bassett M, Dumanovsky T, Huang C, et al. Purchasing behavior and calorie information at fast-food chains in New York City, 2007. Am J Public Health. 2008;98:1457-1459.
30. Shaya F, Flores D, Gbarayor C, Wang J. School-based obesity interventions: a literature review. J Sch Health. 2008;78(4):189-196.
31. The Leopold Center for Sustainable Agriculture. http://www.leopold.iastate.edu/ Accessed Aug. 9, 2008.
32. US Government Accountability Office. GAO-05-458. Chemical Regulation: Options exist to improve EPA's ability to assess health risks and manage its chemical review program. June 2005. Available at: http://www.gao.gov/new.items/d05458.pdf. Accessed Aug. 9, 2008.
33. Wilson M. Green Chemistry in California: A Framework for Leadership in Chemicals Policy and Innovation. Report to the California legislature. 2006. Available at http://coeh.berkeley.edu/docs/news/06_wilson_policy.pdf Accessed Aug. 8, 2008.
34. The Louisville Charter. Available at: http://www.louisvillecharter.org/ Accessed Aug. 8, 2008.
35. UNEP. Strategic Approach to International Chemicals Management. Available at: http://www.chem.unep.ch/saicm/ Accessed Aug. 8, 2008.
36. Kaczynski A, Potwarka L, Saelens B. Association of park size, distance, features with physical activity in neighborhood parks. Am J Public Health. 2008;98:1451-1456.
37. Michaels D. Doubt is their product: How industry's assault on science threatens your health. New York: Oxford University Press, 2008.
38. McGarity T, Wagner W. Bending science: How special interests corrupt public health research. Cambridge: Harvard University Press, 2008.
39. Severson K. Los Angeles stages a fast food intervention. New York Times. Aug. 12, 2008.

ADDENDUM:

Approaches to Healthy Living

Healthy people and healthy communities are interdependent. While we can all make positive choices for personal health, we don't all have equal access to nutritious food, clean air and water, safe workplaces, healthy housing or exercise environments, green spaces, peaceful neighborhoods, or quality health care. In suggesting the following individual approaches, we emphasize that these actions must be combined with community- and society-wide policy changes in order to be truly effective and make healthy living available to all.

As we describe in the previous chapters, key elements of healthy living include these principles:

- Eat healthy and nutritious food;
- Be active physically and mentally;
- Avoid harmful toxicants and pollutants;
- Be socially engaged with family, friends, and community.

WHAT TO EAT? "Eat food (don't eat anything your great grandmother wouldn't recognize as food), not too much, mostly plants."

Michael Pollan, *In Defense of Food: An Eater's Manifesto*

There are many approaches to accomplishing these goals throughout your life. The following is not meant to be comprehensive or complete* but rather offers general suggestions and guidelines, based on evidence reviewed in this report. Taken as a whole, they should help reduce the risks for cognitive decline, Alzheimer's and Parkinson's disease, and illnesses and conditions in the Western disease cluster.

Changing habits is not easy. We nevertheless encourage you to explore where you might start and use the following to help you organize your thinking about how to improve your health and the health of your family. We encourage you to consult the extensive reference list of organizations and publications available on our web site, including our Pediatric Environmental Health Toolkit, at www.psr.org/Boston.

Guidelines for Healthy Nutrition

The following include many of the basics of the "Mediterranean diet." The term is generally used to refer to diets characterized by high intake of vegetables, legumes, fruits, whole cereals, fish, nuts; emphasis on unsaturated fatty acids (including olive oil) and low saturated fatty acids and meat; low-moderate dairy products; and regular moderate ethanol, primarily in the form of wine with meals.[a]

These guidelines set a high bar. They are driven by scientific studies and have not been modified based on practical considerations such as personal taste, ethnicity, cost, or availability. We acknowledge that these recommendations depart somewhat from conventional eating patterns. As such they represent one ideal that people can move toward to the degree they are motivated, rather than expecting to necessarily adopt them as a whole. We also note other evidence-based diets that reduce risks of cardiovascular disease, diabetes, and cancer—for example, the Ornish diet, OmniHeart diets, and diets with higher amounts of protein with varying amounts of fat.[a] *We encourage people to consider other approaches as well, while keeping the critical importance of nutrition in mind.*

1. Healthy living and healthy aging depend on good nutrition from the beginning of life.

- Good maternal nutrition during pregnancy is an important determinant of infant health and child development and helps to reduce disease risk of offspring throughout the lifespan.
- Breastfeeding is superior to formula feeding for both mother and infant and should be strongly encouraged. Among the many benefits, infants who are breastfed have a sharply reduced risk of becoming overweight or obese and developing diabetes.[2 3]
- If using infant formula is necessary, avoid the highest iron supplementation options. Optimal levels of

** This should not be construed as medical advice. People should talk with their healthcare providers if they have any questions or concerns about adopting practices in these guidelines.*

[a] The guidelines are not comprehensive. We explicitly address only targeted issues discussed in the report, though many other nutritional concerns will be incidentally covered by the general pattern of the Mediterranean diet.

iron in infant formula are probably 4–7 mg/L. (See chapter 8.) Use soy formula only if necessary.[b]

- Prioritize healthy and nutritious food for children, teenagers, and adults. Consumption of fast food and calorie-dense snacks is associated with increased caloric intake, weight gain, and obesity and should be reduced or eliminated. [4 5 6 7]

2. Eat lots of fresh fruits and vegetables, especially deep-green and orange vegetables, a serving of each with every meal if possible. Fruits and vegetables provide essential antioxidants, vitamins, and other critical micronutrients. Many green vegetables contain small amounts of healthy omega-3 fatty acids, which add up to make a difference.

3. Avoid saturated and trans fats. Use vegetable oils that have a healthy balance of omega-3s, omega-6s, and monounsaturated fat.

- Avoid saturated fats by eating a predominantly plant-based diet, or consuming non-fat or low-fat varieties of dairy, lean meat, and chicken.
- Avoid frequent or routine use of oils high in omega-6s—especially corn, safflower, sunflower, and peanut oils. Avoid fast foods, which can be high in trans fats and omega-6s, and processed food, which is often high in omega-6s.
- Increase canola oil (a better balance of omega-3s and 6s) and olive oil (high in monounsaturates). Substitute these for butter, which is high in saturated fat, or margarine, which may be high in omega-6. Walnuts, flaxseed, and their oils are also high in omega-3s. Avoid hydrogenated and partially hydrogenated oils, usually listed on package labels.

4. Eat foods high in omega-3s.

- Eat fish at least once a week. Fish are a good source of omega-3s and other micronutrients, but those that are high in contaminants such as mercury and PCBs should be avoided. Cod, haddock, and pollock are among the low-fat, low-mercury choices. High-mercury fish include swordfish, king mackerel, albacore tuna, and tilefish. Canned light tuna can be safely eaten as often as once a week. Wild Alaskan salmon —fresh, frozen or canned—is an excellent source of omega-3s and may safely be eaten on a weekly basis. For detailed fish consumption recommendations, see PSR's *Healthy Fish, Healthy Families* at http://www.arhp.org/files/healthyfishhealthyfamilies.pdf . If you don't eat fish, consider taking fish oil or algae-derived long-chain omega-3s. If using fish oil, chose a brand that has been distilled to remove toxicants.

5. Avoid routine consumption of sugars including table sugar, high fructose corn syrup, maple syrup and honey, and beverages and foods containing them.[c] (Read the labels.) These foods cause rapid elevations of blood sugar, which has been linked to obesity, type II diabetes, cardiovascular disease, and related illnesses.

6. Consume low-glycemic carbohydrates that do not cause rapid, high blood sugar elevations—mainly unrefined, complex carbohydrates rather than refined/processed grain:

- Decrease—refined grain–based products including cakes, cookies, crackers, bagels, non whole-grain breads, corn chips, refined breakfast cereals, and so forth. These are generally high-glycemic foods.
- Increase—whole grains (especially pearled barley, steel-cut oats, rye, buckwheat, brown rice), legumes (as noted below), fruits, non-starchy vegetables, pasta, winter squashes, tubers (yams, sweet potatoes) These are low-to-moderate glycemic foods.
- Increase legumes—such as chickpeas, lentils, and soybeans. Legumes are an excellent source of high-quality carbohydrates (with low glycemic index) as well as protein and micronutrients.
- Information about the glycemic value of a wide variety of foods can be found at the glycemic index database at www.glycemicindex.com.The glycemic index (GI) for a given food is interpreted as follows: 55 or less = low GI, 56-69 = medium GI, 70 or more = high GI

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[b] *Concerns about high manganese levels in soy formula are based on the limited data discussed in chapter 8. Evaluations of the safety of soy formula by expert panels have concentrated on potential impacts of phytoestrogens in soy on sexual maturation and reproductive tract development. They have not considered the potential impacts of excessive dietary manganese during infancy on childhood learning and behavior or later neurodegenerative disease.*

[c] *This recommendation is based on the metabolic response to sugar. Honey, however, has anti-oxidant properties and is likely to be preferable when small amounts of sweeteners are used. Many foods and beverages contain added high fructose corn syrup or refined sucrose and should be avoided.*

7. Get food from local and organic sources whenever possible—co-ops, CSAs (Community Supported Agriculture), community gardens, family farms. Local food is fresher and more likely to be harvested when ripe, increasing the value of protective antioxidants and micronutrients. Eating locally also reduces energy required to transport food, thereby reducing greenhouse gas emissions. Purchasing locally helps build local food production capacity, increasing food security in the face of rising food-transportation costs and climate change. Eating organic foods will reduce your exposure to pesticides.

8. Drinks and Liquids

- **Alcohol** – Evidence supports **modest consumption** of ½–2 drinks a day for adults as routine prevention, though alcohol intake should be avoided in risk situations including pregnancy and driving motor vehicles. Higher levels of consumption increase the risk of heart, liver, brain diseases, and some kinds of cancer and should be avoided. Red wine has important antioxidants, including flavonoid polyphenols, though the evidence does not show a consistent benefit for red wine over other forms of alcohol.
- **Green tea** is high in polyphenols.
- **Caffeine** may reduce the risk of Parkinson's disease.

9. Other

- **Other foods high in polyphenols which are neuroprotective.** These include curcumin (found in the spice tumeric).
- **Food additives to avoid**
  - **Aluminum**

  Recent evidence reopens a debate about whether dietary aluminum may increase the risk of Alzheimer's disease. The data are limited and considerable uncertainty remains. Nevertheless, if you want to limit potentially excessive intake, avoid routine consumption of foods with aluminum-containing baking powder or SALP (sodium aluminum phosphate), an additive used in some grain-based products and some processed cheeses. Highest aluminum levels in food have been reported in some pancake and waffle products—including mixes, frozen and restaurant varieties. Smaller amounts have been reported in baking mixes for some cakes, biscuits and muffins, and in the crust and cheese of some frozen pizza. These products account for the bulk of dietary exposure.[8 9 10] Aluminum additives are not always listed on the ingredient labels of baking supplies and products (including pancakes and waffles).

Reduce Exposure to and Generation of Toxicants

Exposures to some environmental chemicals can increase the risk of a number of different diseases, including those discussed in this report. Since environmental chemicals are so pervasive in our lives and exposure levels differ from person to person, it is virtually impossible to lay out guidelines that will be universally applicable. Therefore, we simply suggest here an approach to reducing your exposure to toxic chemicals and substances such as pesticides, metals and solvents and recommend consulting more comprehensive resources for additional details relevant to your specific circumstances. This analysis will also help you understand how you can minimize what you put back into the air, water and soil of the ecosystem. First, consider the following framework for understanding toxic exposures:

- ***Where*** you can be exposed to toxic substances including home, school, daycare facilities, workplace, community, hospitals and other care facilities;
- ***How*** you can be exposed via food, air, water, and soil;
- ***At what times*** you can be exposed, including seasonally, during special projects such as home renovations, or while engaging in gardening, hobbies, etc.
- ***Which products you buy and use that may result in exposures,*** including those for cleaning, personal care, lawn and garden maintenance, on your pets, and when renovating your home.

Next, here are some steps you can take to address major potential routes of exposure:

1. Inventory your home for hazardous materials you may be using for home cleaning and maintenance, lawn and garden care, personal care, and pet care. Dispose of these hazardous materials properly and replace with less-toxic alternative products or processes. Avoid hazardous exposures to toxicants such as lead and solvents during building and remodeling projects. Use "green" building materials, or those that are less toxic from manufacture to disposal.

2. Assess drinking water quality via water testing (for well water) or community water reports, and filter if necessary. The appropriate approach to filtration will depend on the specific contaminants identified.

3. Eliminate or reduce pesticide use in the home and on lawns and gardens. Adopt "Integrated Pest Management" techniques which include a variety of measures to prevent or eliminate pests.

4. Reduce consumption and waste, recycle materials, and conserve energy. You can further reduce fossil fuel consumption and air pollution by using public transportation and walking and biking when possible.

5. Assess workplace, school, community and care facilities for sources and nature of hazardous exposures. Work with the appropriate people to reduce use of toxicants.

Physical, Social and Mental Activity, Stress Reduction

Rationales for regular physical exercise, reduction of excessive stress, and rich social engagement are well established in the medical literature. Preliminary evidence and common sense also suggest benefits of challenging and engaging mental activity. While many different approaches are possible within each category, information comparing one to another is often lacking, and their relative advantages remain uncertain. Nonetheless, based on evidence that is available the following general guidelines are worth following:

1. **Physical Exercise**—Increasing physical activity at any age improves physical and emotional wellbeing. Walking more each day can improve health, prevent overweight and obesity, and help maintain independence. All family members should adopt daily exercise habits daily. Children should be encouraged to play outdoors (except where safety issues interfere). Keep active as much as possible. Choose stairs over the elevators or escalators. Walk or bike for transportation whenever possible. Move more around your home or workplace. Daily aerobic exercise, as moderate as brisk walking, for at least half an hour, is very beneficial.

2. **Social, Family, and Community Activity**—is good for you and the broader community. Regular social engagement with others reduces the risk of cognitive decline in later years. Volunteer, get involved in community activities, stay in touch with family members.

3. **Reducing Stress**—is important. Many activities have not been adequately studied for their potential benefits, but some that have been addressed in this report including regularly ***interacting with nature.*** A recent review of the literature on meditation or ***mindfulness-based stress reduction*** (MBSR) also concluded that it is "a safe, effective, integrative approach for reducing stress. Patients and healthcare providers experiencing stress or stress-related symptoms benefit from MBSR programs."[11] It requires no special equipment or financial investment, just an inclination to sit in a quiet place and try to calm the mind. ***Yoga*** has been practiced for thousands of years. It can be done anywhere there is a flat surface, and requires no special equipment. Practitioners worldwide attest to its mental and physical benefits.[12 13] Take time out to relax. Many of us are constantly expected to multitask and respond instantly to ever more rapid communications. Try to find even a few minutes a day to relax.

4. **Mental Activity**—Exercising your brain may be beneficial for maintaining healthy cognition. Common sense ways to do this include crossword puzzles and word games, chess, and activities that require critical thinking. Such activities exercise your brain and may help keep it fit.[14 15]

Endnotes

1 de Souza R, Swain J, Appel L, Sacks F. Alternatives for macronutrient intake and chronic disease: a comparison of the OmniHeart diets with popular diets and with dietary recommendations. Am J Clin Nutr. 2008;88(1):1-11.

2 Gunderson E. Breast-feeding and diabetes: long-term impact on mothers and their infants. Curr Diab Rep. 2008;8(4):279-286.

3 Plagemann A, Harder T, Franke K, Kohlhoff R. Long-term impact of neonatal breast-feeding on body weight and glucose tolerance in children of diabetic mothers. Diabetes Care. 2002;25(1):16-22.

4 Bowman S, Gortmaker S, Ebbeling C, et al. Effects of fast-food consumption on energy intake and diet quality among children in a national household survey. Pediatrics. 2004;113(1 pt 1):112-118.

5 McCrory M, Fuss P, Saltzman E, Roberts S. Dietary determinants of energy intake and weight regulation in healthy adults. J Nutr. 2000;130(2S Suppl):276S-279S.

6 McCrory M, Fuss P, Hays N, et al. Overeating in America: association between restaurant food consumption and body fatness in healthy adult men and women ages 19 to 80. Obes Res. 1999;7(6):564-571.

7 Maffeis C, Grezzani A, Perrone L, et al. Could the savory taste of snacks be a further risk factor for overweight in children? J Pediatr Gastroenterol Nutr. 2008; 46(4):356-358.

8 Saiyed SM, Yokel RA. Aluminium content of some foods and food products in the USA, with aluminium food additives. Food Addit Contam. 2005 Mar;22(3):234-44.

9 European Food Safety Authority. Safety of aluminium from dietary intake. Scientific Opinion of the panel on food additives, flavourings processing aids and food contact materials. EFSA Journal. 2008:754:1-4.

10 Pennington JA, Schoen SA. Estimates of dietary exposure to aluminium.Food Addit Contam. 1995 Jan-Feb;12(1):119-28.

11 Praissman S. Mindfulness-based stress reduction: a literature review and clinician's guide. J Am Acad Nurse Pract. 2008 Apr;20(4):212-6

12 Yadav RK, Ray RB, Vempati R, Bijlani RL. Effect of a comprehensive yoga-based lifestyle modification program on lipid peroxidation. Indian J Physiol Pharmacol. 2005 Jul-Sep;49(3):358-62.

13 Bijlani RL, Vempati RP, Yadav RK, Ray RB, Gupta V, Sharma R, Mehta N, Mahapatra SC. A brief but comprehensive lifestyle education program based on yoga reduces risk factors for cardiovascular disease and diabetes mellitus. J Altern Complement Med. 2005 Apr;11(2):267-74.

14 Wilson RS, Scherr PA, Schneider JA, Tang Y, Bennett DA. Relation of cognitive activity to risk of developing Alzheimer disease. Neurology. 2007 Nov 13;69(20):1911-20. Epub 2007 Jun 27.

15 Albert, MS. Changing the trajectory of cognitive decline? N Engl J Med 357:5502-3.


OUTCOMES
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growth and development
disease
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pathways
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