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.”

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.
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. 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.

Inflammation is now emerging as a unifying theme in the chronic diseases of western society. (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.” Another key study in 2003...
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. 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. 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. Individuals with metabolic syndrome have markedly increased risks for developing type II diabetes and coronary disease.

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. 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.

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

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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. 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. 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, metabolic syndrome, obesity, neurodegeneration, depression, and osteoporosis.

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...
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.

**Inflammation in the Brain**

Inflammation in the brain 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.  

**Oxidative Stress**

Oxidative stress is closely related to the process of oxidative stress. Like inflammation, oxidative stress also increases in aging and especially in neurodegenerative diseases like Alzheimer’s 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 in the body, an organ system, or tissue.
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. 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.

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. This takes place primarily in mitochondria, the major site of oxygen utilization in the cell, where fuel is burned and energy is produced.

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, 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**

As mentioned above, the brain is particularly susceptible to oxidative stress because it has a relative lack of antioxidant systems.
an abundance of readily oxidizable fatty acids, and high oxygen utilization leading to increased production of ROS.\textsuperscript{45, 46} In addition, the brain contains relatively high levels of transition metals\textsuperscript{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\textsuperscript{48} or by binding amyloid-beta and catalyzing the production of ROS.\textsuperscript{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.\textsuperscript{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.\textsuperscript{53-57}

**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.\textsuperscript{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. 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. 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, and ROS/inflammation causing amyloid-beta production—evidence increasingly suggests that oxidative stress and inflammation commonly initiate this process.

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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*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.

*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. 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.

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.
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

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, whereas 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

Types of Fatty Acid

- **Saturated fat**
  - Fish
  - Canola, flax seeds
  - Green vegetables
  - Products from grazed animals
  - Eggs from flax-fed chickens

- **Unsaturated fat**
  - Fast & processed food
  - Grain-fed animal products
  - Corn, soy, sunflower
  - Safflower, peanut oils

- **PUFA**
  - Olive oil

- **MUFA**
  - Fish
  - Canola, flax seeds
  - Green vegetables
  - Products from grazed animals
  - Eggs from flax-fed chickens

The listed foods are particularly good sources for the fatty acid family under which they are listed. In some cases, the food may provide some of both omega-3 and omega-6 fatty acids.
pasture have increased levels of omega-3 fatty acids. Other sources of saturated fats include baked goods, cheese, milk, margarine and butter.

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. Omega-6s can also have anti-inflammatory effects—by giving rise to less prominent anti-inflammatory eicosanoids 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.

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

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<th>Omega-3</th>
<th>Omega-6</th>
<th>Saturated</th>
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<tr>
<td>Food system properties</td>
<td>Perishable</td>
<td>Durable</td>
<td>Increased in factory farmed animal products</td>
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<td>Short shelf life</td>
<td>Processed foods</td>
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<td>Long shelf-life</td>
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<td>Immune properties</td>
<td>anti-inflammatory</td>
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<td>Evolutionary context</td>
<td>recent marked decline</td>
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*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.*
The portion of LPS that causes most biological activity, lipid A, contains saturated fat. If the saturated fat is removed from LPS, the LPS is no longer immunologically active, causing a complete loss of endotoxic activity. 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.

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. 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. 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. These observations, among others, underscore the important and complex interconnections between diet, the intestine, and the immune system.

1 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.

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. 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.

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1 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. 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, 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:

- 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.

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

k VLDL is the abbreviation for very low density lipoprotein.
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 Diagram](image)

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 (Foxa2, Foxo1). When activated, these promote synthesis of saturated fat and triglycerides 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.97 One of the key implicated signaling proteins is JNK, 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.98

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1 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.

2 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.

3 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 (phosphatase 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.

4 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.

5 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. 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.

Recent evidence demonstrates that nonmicrobial substances can also activate TLRs or may heighten the TLR response to a pathogen. In particular, a substantial body of evidence (summarized by Lee and Hwang 2006) 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. Other poly- and monounsaturated fats also inhibit TLR activation, though they are far less effective than omega-3 fatty acids.

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. 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.

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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.

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 disease.

**TLR4, TLR4-Ligands & Chronic Disease**

**A Summary of Selected Evidence**

- *Increased insulin resistance in children & adults* Kaitossan, Reuter, Veisby
- *Increased cardiovascular risk* Hu, Hu, Ascherio
- *Increased Alzheimer’s disease & cognitive decline* Morris, Morris

- *In vitro inflammation* Lee
  - Systemic Insulin resistance in vivo Shi (lipid mixture)
  - Vascular inflammation, insulin resistance, & decreased eNOS in mice Kim
  - Decreased insulin signaling & NO production in human microvascular endothelial cells Kim

- Loss of function TLR mutation inhibits microglial activation by amyloid-beta, resulting in lower release of IL-6, TNF, & NO, in vitro Walter
  - Increased atherosclerosis in an animal model Michelsen, Pasterkamp
  - Hypoactive TLR4 variant associated with decreased coronary artery disease Balestrieri, Ameziane
  - Vascular inflammation, diabetes Kolek
  - Carotid atherosclerosis Kiechl & late onset Alzheimer’s disease Minoretti

- LPS triggers TLR4-mediated neurodegeneration in vivo (mice) and in vitro Lehmann

- Adult and prenatal exposure to systemic LPS triggers (mediated via TNF alpha) chronic neuroinflammation & dopaminergic degeneration, in vivo. Qin, Ling
This relatively new dietary pattern contributes to a cascade of inflammation, insulin resistance, dyslipidemia, and vascular 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. 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.

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 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.

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. 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.

\[1\] This evidence includes metabolic studies, short- and medium-term randomized trials, and long-term epidemiologic observations.

\[2\] 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.

\[3\] 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. 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.

* 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.\(^ {164}\)

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,
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), in turn, is triggered by immune stimulation, which increases the production of PGs. 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. Metabolism of omega-6 arachidonic acid by the 5-lipoxygenase enzyme (LOX) produces the leukotriene (LT)4 series. LTB4 increases vascular permeability, leukocyte chemotaxis, and increased production of reactive oxygen species and inflammatory cytokines like TNF-α, IL-1 and IL-6. Other LTs of this series are bronchoconstrictors and are implicated in the pathogenesis of asthma. 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.

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.

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.

Other 4-series leukotrienes include LTC4, D4 and E4.

Leukotriene inhibitors (such as montelukast, zafirlukast, or zileuton) are commonly used for long-term asthma control.
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, though not all studies are consistent. 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. This hyperinsulinemic effect is a significant public health concern. 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.) 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.\textsuperscript{174, 175}

Inadequate exercise is also associated with inflammatory-metabolic effects.\textsuperscript{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.\textsuperscript{177} The net result is a decrease in oxidative damage.
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.\textsuperscript{178}

Similarly, obesity is associated with increased inflammatory markers, possibly due to the increased secretion of inflammatory cytokines by adipose tissue.\textsuperscript{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.\textsuperscript{180}

Air pollution\textsuperscript{181-184} and psychosocial stress\textsuperscript{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\textsuperscript{188} and a 91 percent lower risk for the development of diabetes type 2 among women\textsuperscript{189} in long-term observational studies. Clinical intervention studies, (including several randomized studies\textsuperscript{190-192}), have demonstrated reductions of approximately 50 percent in diabetes\textsuperscript{193} and associated mortality\textsuperscript{194} with diet and lifestyle intervention. Consumption of a Mediterranean-type diet by heart attack patients reduced recurrent heart attacks by 70 percent\textsuperscript{195} and mortality by nearly 50 percent\textsuperscript{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.\textsuperscript{197 198}

**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.
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