

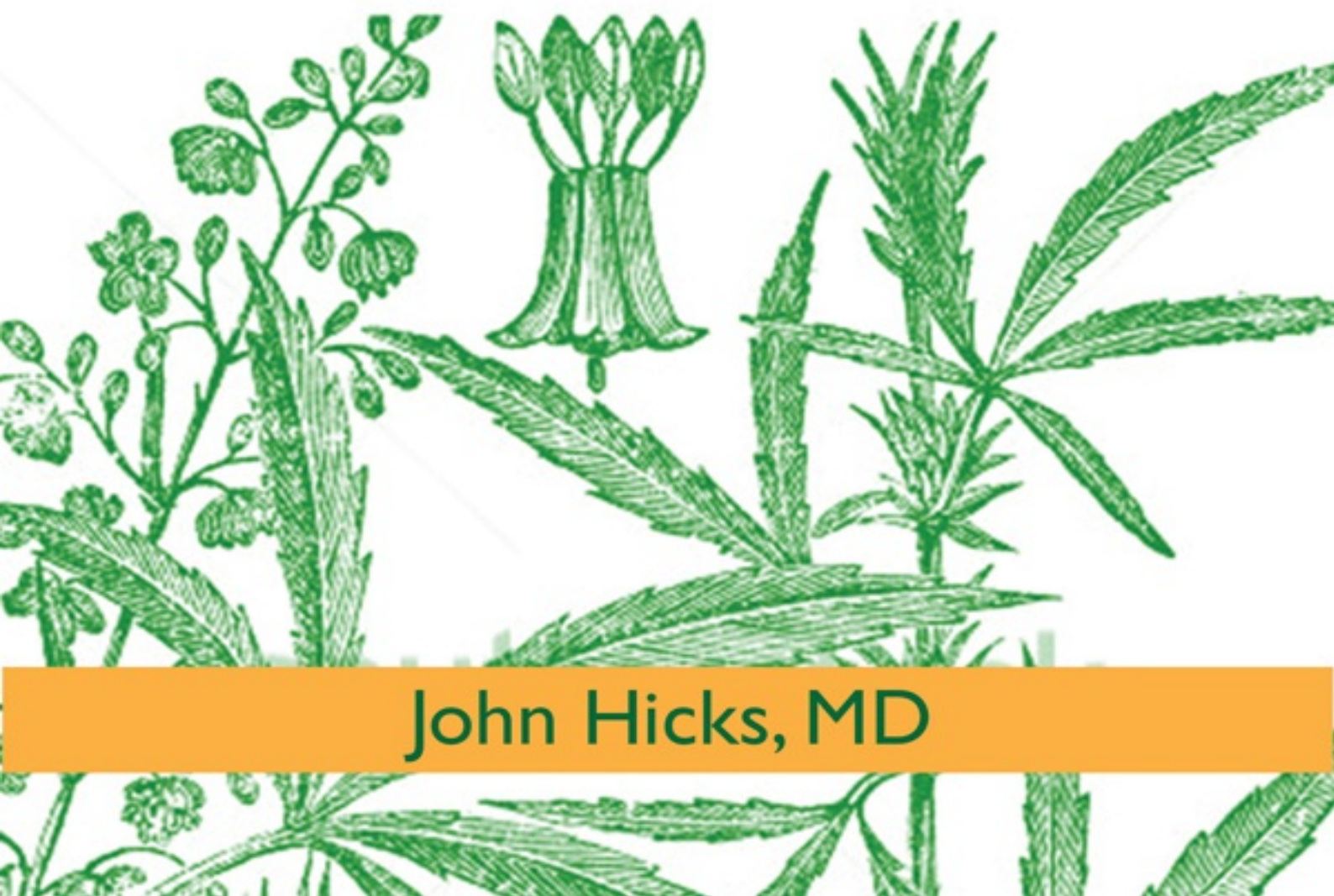
*Using a Natural Herb to Heal Arthritis,
Nausea, Pain, and Other Ailments*

THE

MEDICINAL
POWER

OF

CANNABIS



John Hicks, MD

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John

I

History of Hemp

Hemp, from the plant *cannabis sativa*, and its sister plants, *cannabis indica* and *cannabis ruderalis*, has a rich and varied history of use, including hemp fibers for textiles, the oil, the seeds for medicine and, of course, the plant itself for psychotropic activity. Although the exact date of its first use is unknown, records and artifacts indicate that hemp has been cultivated for more than 10,000 years.

We know that hemp has been cultivated in China since 4000 BCE. The first identified paper, in China around 1000 BCE, was made from hemp. It was very white and extremely durable, lasting for long periods of time without decomposing.¹ Hemp cords in pottery from Mesopotamia date back over 10,000 years, and fabrics made with hemp have been dated to 8000 BCE in what is now modern Taiwan, as well as textiles found in China and Turkestan dated around 4000 BCE. In the book *The Natural History*, Pliny the Elder describes the use of hemp rope, and of marijuana providing analgesic effects. In the years between 2000 and 800 BCE, the plant was recorded in the Hindu sacred text Atharvaveda as sacred grass; it was considered one of the five sacred plants in India, used both medicinally and for rituals and ceremonies. Psychotropic properties were first described between 100 BCE and 1 CE, reported by Chinese herbalist Pen Tsao Ching. In 600 BCE, the Zend-Avesta, the sacred book of Zoroastrianism, spoke of hemp's intoxicating resin being used by the people of India.

Thousands of years later, between 1606 and 1632 AD, the French and British cultivated cannabis for hemp in their colonies at Port Royal, Acadia

(present-day Nova Scotia). In 1611, the British began growing it in Virginia, and by 1632 it was also grown in Plymouth, Massachusetts.⁴ Hemp was used to make rope and sails for shipping and navy fleets. The colonies passed laws to encourage the production of hemp, as it was also needed for cordage and cloth. In the 1630s in Hartford, Connecticut, the colonists passed a resolution requiring every family to plant hemp.

During the 1700s, the American colonists were forbidden to weave with hemp, which kept them tied to England to purchase woven products. New England, Virginia, Pennsylvania, New York, New Jersey, and North and South Carolina were paid subsidies to grow hemp, or they were given tax credits to do so. Hemp was also used as money.^{2,4} The weaving restrictions ended when Irish weavers settled in the colonies and taught the colonists their trade, beginning the production of hemp fabrics there.¹⁸⁴ Decades later, during World War II, hemp was grown to provide needed rope for the United States Navy. The loss of the Philippines and their Manila hemp was met by renewed US efforts to produce hemp, and the US Department of Agriculture (USDA) produced films to stimulate its production for war use. Farmers and their sons who grew hemp from 1942–1945 were waived from serving in the military.³ Hemp was used for clothing, military uniforms, ships' rigging, shoes, parachute webbing, baggage and more.³ In 1943, during World War II's Hemp for Victory campaign, production grew from approximately 2,000 acres to about 146,200 acres.³

Thousands of years after the Chinese made paper from it, cannabis hemp was used as legal tender (money) in most of the Americas between 1631 until the early 1800s.¹ Benjamin Franklin started one of America's first paper mills with cannabis,^{3,4} and both George Washington and Thomas Jefferson grew cannabis on their plantations.^{3,4} Jefferson drafted both the Declaration of Independence and the Constitution of the United States on hemp paper.^{3,4} In Europe, artists Rembrandt and Van Gogh painted on canvas made of hemp.

In 1916, the chief scientists of the USDA, Jason L. Merrill and Lester H. Dewey, created paper from hemp pulp, showing that it was environmentally better than wood pulp and would reduce the need for deforestation as well as the toxic chemicals released into the environment. They demonstrated that hemp pulp uses between one-seventh and one-fourth as much sulfur-based acid chemicals as wood pulp and would thereby prevent the constant release of dioxins from the production of paper. By using hemp instead of wood, hydrogen peroxide was effective as a less toxic substitute for chlorine bleach.

However, history shows us that dollars replaced common sense, and the powerful industrialists realized that the cultivation of cannabis stymied their monetary gain as long as it remained in competition with the wood-paper industry. In 1914, the Harrison Act in the United States defined the use of marijuana, among other drugs, as a crime.⁶ The historical legacy is that today hemp is only legal to grow in California and Colorado and is heavily regulated; restrictions include limiting how it's grown, how the fields are fenced, lighting requirements, and the use of guards. If these restrictions were loosened, one could certainly make the case that hemp could replace wood-pulp paper, computer printout paper, corrugated boxes, and paperback books with significantly fewer adverse repercussions to the environment.

The head of the industrialists was William Randolph Hearst, who had large timber holdings that fed his paper industry and, in turn, his powerful newspaper industry. William DuPont, another influential industrialist, had a huge petrochemical industry, creating plastics, paints, and other fossil fuels. Andrew Mellon, the United States Secretary of the Treasury and owner of Gulf Oil, had a vested interest in the competitive threat of hemp cultivation and created tax breaks for the oil companies, such as the oil-depletion allowances that are still in force today. Mellon also pushed through tax plans that reduced taxes on wealthy and large corporations to encourage greater investment.

These forces combined to make hemp the object of the first “yellow” journalism.⁷ To protect their interests and fortunes, these men worked

with elements of government to condone and popularize movies, publications, and books about the evils of marijuana. Propaganda about marijuana had originated in Mexico, where it was banned in 1920, and found a home north of the border when Harry Anslinger, the director of the US Narcotics Bureau, began to push the theme of “reefer madness.” Ainslinger, with the support of the Hearst and DuPont empires, easily convinced states to begin outlawing marijuana. He testified in Congress about the dangers of “this evil weed” in 1937, wrote editorials and letters in multiple papers, and convinced the Congress to pass the Anslinger Act. Formally known as the Marihuana Tax Act of 1937 (HR 6385), the law imposed a prohibitive tax on the importation and cultivation of hemp and hemp products and effectively criminalized marijuana use at not only state but federal level. In addition, legislation was pushed through Congress that gave tax breaks to the oil companies, to make the industrialists happy.⁷

The medical history of marijuana dates back to Emperor Chen-Nung of China,¹ who recorded the first use of cannabis as medicine in the year 2737 BCE. Those records indicate that cannabis was used to treat malaria, female disorders, and many other illnesses for more than 5,000 years. The herbalist emperor described the fruit *Ma-fen* and explained that if this fruit were taken in excess, it would produce hallucinations.^{1,2} During the years between 2000 and 800 BCE, the Hindu sacred text Atharveda referred to the plant as *sacred grass*. Considered one of the five sacred plants in India, it was used both medicinally and ritualistically in ceremonies. In 600 BCE the Zend-Avesta spoke of hemp’s intoxicating resin and its use by the Indian people. Psychotropic properties of the plant and its use were first described between 100 BCE and 1 CE, reported by Chinese herbalist Pen Tsao Ching.

Between 130 and 200 AD, Greek physician Galen prescribed medical marijuana.¹ In 200, the first pharmacopeia listed medical marijuana, and on the other side of the world, the Chinese surgeon Hrea To used marijuana as an anesthetic. In 300 AD, a young woman in Jerusalem received medical marijuana to aid childbirth. On the European continent, French physicians mentioned the use of medical marijuana in 1532 AD,¹

and, in 1563, a Portuguese physician mentioned the medicinal effects of marijuana in his medical practice.¹ In 1578 China's Li Shih-Chen wrote of the antibiotic and antiemetic effects of medicinal marijuana.¹ Robert Burton, the seventeenth-century British writer, listed marijuana as a treatment for depression in his 1621 book *Anatomy of Melancholy*.¹

More than one hundred years later, in 1764, medical marijuana appeared in New England dispensaries as a prescription option.¹ The Edinburgh New Dispensary of 1794¹ listed hemp oil as useful for coughs, venereal disease, and urinary incontinence. During the 1840s in America, medicinal preparations with the cannabis base were available through this dispensary.⁶ During the mid-nineteenth century, medical marijuana was used to treat rabies, rheumatism, epilepsy and tetanus; in 1842, Irish physician O'Shaughnessy published cannabis research in English medical journals.^{1,2} The United States added cannabis to the pharmacopeia in 1850, and, from then until 1915, marijuana was widely used in the United States as a medicinal drug and could be easily purchased at pharmacies and general stores. In England, Sir J. R. Reynolds, chief physician to Queen Victoria, prescribed medical marijuana for her in 1890.¹

In the United States between 1915 and 1927, cannabis began to be prohibited for nonmedical use. The government said that it had no medical benefit and could therefore no longer be used for those reasons. Industry was using imported hemp for some products and gradually replaced all US-grown hemp as the rules became too restrictive. Prior to the ban, by 1915, 8,400 acres of hemp were grown in the United States. Kentucky had 6,500 acres, and 2,000 acres were grown among Ohio, Indiana, Wisconsin, and California.³ In 1915 California was the first state to ban cannabis, followed by Texas in 1919 and New York in 1927.

As noted earlier, in 1936, the propaganda film *Reefer Madness*, which was meant to scare American youth, was released.³⁰⁶ The film depicted the dangers of marijuana consumption, vilified those who "pushed" it on unsuspecting youth, and dramatized its hallucinatory effects, with

characters driven to rape, suicide, hit-and-run accidents, and even insanity. One year later, Congress passed the Marihuana Tax Act, even after Dr. William C. Woodford testified for the American Medical Association (AMA) at the congressional hearings, stating that the AMA knew of no evidence proving marijuana to be a dangerous drug. He further stated that, in effectively prohibiting its use, lawmakers were losing sight of the fact that future investigations might show that there are substantial medical uses for cannabis.^{2,3} The law that was passed required a \$100 transfer tax (\$1,664.63 in 2014 dollars) on the sale of marijuana, making it financially prohibitive and ensuring the financial advantage to Hearst, DuPont, and Mellon.

Despite the tax, during the 1930s, Ford Motor Company saw a future for biomass fuels and operated a biomass conversion plant that used hemp. They extracted many compounds from the plant that are still used and owned by oil-related industries.⁷ In 1941 Ford produced an automobile from hemp-based plastics that was both lightweight and suffered less damage when involved in a crash.⁴ This automobile was also fueled by clean-burning, hemp-based methanol.^{3,4} It was known that hemp oil could also produce high-grade diesel fuel, aircraft engine fuel, and high-grade machine oil, an easily renewable source of energy and clean-burning fuel. Methanol is used today in some race cars.¹

By 1941 cannabis was removed from the *United States Pharmacopeia*, and its medical uses were no longer recognized in America.¹ The Boggs Act and the Narcotics Control Act in 1951 increased all drug penalties and laid down mandatory sentences for those convicted.⁷ The National Organization for the Reform of Marijuana Laws (NORML) was formed in 1970, and, in the Comprehensive Drug Abuse Prevention and Control Act, the law replaced mandatory penalties for drug offenses for marijuana and categorized them separately from narcotics.⁷

The Shafer commission recommended that the use of cannabis be relegalized in 1972, but its recommendations were ignored.⁷ Even the scientist Carl Sagan proposed that marijuana may have been the world's

first agricultural crop, leading to the development of civilization itself. In 1977 he wrote that “it would be wryly interesting if in human history the cultivation of marijuana led generally to the invention of agriculture, and thereby to civilization.”⁵

The drug nabilone, a cannabinoid-based medication, was released in 1975.⁸ nabilone is a synthetic cannabinoid, most like delta-9-tetrahydrocannabinol (delta-9-THC), used for cancer chemotherapy-induced nausea and vomiting (CINV) and as an adjuvant for the treatment of neuropathic pain. Used in Canada, the United States, the United Kingdom and Mexico, it is produced by several companies and was FDA-approved in 1985 as dronabinol, a synthetic form of THC for cancer patients.⁸ In 1986 the federal government created the Compassionate Investigational New Drug (IND) research program that allowed patients to receive up to nine pounds of cannabis from the federal government each year. Marijuana was still maintained as a Schedule 1 drug, which reflected its “high potential for abuse and no medical value.” President Reagan implemented the Anti-Drug Abuse Act, which mandated minimum sentences and increased federal penalties for possession and distribution of marijuana, instituting the United States’ international War on Drugs.

Despite the political climate, in 1988 the US Drug Enforcement Agency (DEA) administrative law judge Francis Young presented his findings and, after thorough hearings, found that marijuana had a clearly established medical use and recommended it be reclassified as a prescriptive drug. His recommendation was ignored.⁹ The US government closed the Compassionate IND. However, in 1992, pressure mounted and dronabinol was approved for AIDS wasting syndrome.⁴⁷⁶ Questions were raised about the pharmaceutical industry’s influence and their desire to stifle competition from marijuana.

In 1996 California became the first state to really use medical marijuana, and it was legalized for people who suffer from AIDS, cancer, and other serious illnesses. This was followed by legalization in Arizona, Colorado, Maine, Montana, Nevada, Oregon, Washington, the District of Columbia,

Hawaii, Maryland, New Mexico, Rhode Island, and Vermont.⁷ One year later, in 1997, the American Office of National Drug Control Policy commissioned the Institute of Medicine (IOM) to do a comprehensive study of medical efficacy in cannabis therapeutics. Their conclusions were that cannabis is safe and effective, that medical patients should have access to it, and that government should expand funds for further research and drug development of marijuana. The federal government ignored these findings and refused to act on the recommendations of this study.¹⁰ In 2001 Canada adopted federal law in support of medical marijuana, the first country in the world to approve medical marijuana nationwide.⁷

Meanwhile, in the United States, President Bill Clinton contradicted the IOM recommendations in 1997 and 2001 and continued with Reagan and George H. W. Bush's War on Drugs.⁶ He continued a campaign to arrest and prosecute medical-marijuana patients and the medical providers and dispensaries in California and elsewhere. In 1999, the DEA reclassified dronabinol to a Schedule 3 drug, which made it easier to prescribe, but marijuana was still listed as a Schedule 1 drug.⁵¹⁶ Between 2001 and 2009, the George W. Bush administration intensified the War on Drugs, targeting both patients and doctors across the state of California.⁶

As of this writing, the entire area of marijuana and its legality is in a state of constant flux. New legislation is presently being considered to change the whole access and recommendations for the medical use of marijuana in California and other states. The California Medical Board is getting ready to change their position and rules regarding appropriate recommendations for the use of medical marijuana, but it appears that a state of flux will be ongoing.

II

Inflammation

Medications developed to control inflammation have not been effective and have many side effects. Research on marijuana shows that it works to reduce inflammation both locally and generally this is accomplished through actions on different cell types as well as effects on the immune system. We are going to see that the effects and benefits of marijuana are diverse and affect inflammation in many areas of the body, thereby helping with different diseases.

Inflammation underlies most diseases of today and needs to be modulated if we are to help control acute and chronic symptoms of disease. The word *inflammation* is derived from the Latin *inflammo*, or “to set alight.” The inflammatory response is a normal one, controlled by the immune system to deal quickly and effectively with issues. Chronic inflammation ensues when the immune system is out of balance.¹ Our immune system has two sides, the TH1 side and the TH2 side. Composed of cytotoxic T cells and natural killer cells, the TH1 side helps fight viruses and fight cancer. The TH2 side of the immune system helps produce antibodies for our protection.^{1, 2}

Inflammation is the response of a tissue to injury by direct trauma, irritants, toxins or pathogenic organisms such as viruses and fungi. In inflammation, blood flow increases to the tissue, as does temperature, redness, swelling, and pain. Depending on the source of the trauma, the response of tissues and the immune system will be specifically tailored to the precipitating cause.^{3, 4} Pain, heat, redness, swelling, and the loss of

function are the cardinal signs of inflammation.²⁰ Originally described by Celsus (c. 25 BCE to c. 50 CE), the original four cardinal signs were pain (*dolor*), heat (*calor*), redness (*rubor*), and swelling (*tumor*). The fifth sign, loss of function, was added by Galen in the second century CE.²¹

When the immune system is activated by bacteria, it occurs through specific bacterial surface antigens. Each bacterium has its own specific antigens. Antigens on the bacteria can also activate the complement system through the alternative pathway. Antigens, which are cell specific markers, can activate the complement system and be destroyed. When activated, the complement system helps destroy the bacteria by punching holes in the cell walls of the bacteria. Other antigens on pathogens form a pathogen-associated molecular pattern (PAMP). These antigens react with immune cells, such as leukocytes and macrophages. This interaction leads to the activation of the leukocytes through these antigens reacting with specific, toll-like receptors (TLR). The mast cells are the major tissue inhabitants from the immune system, living in the tissues and responding to the introduction of pathogens.^{5, 6}

The cytoplasm of the mast cells in the tissue is loaded with granules containing mediators of inflammation. The surface of the mast cell is coated with receptors. When the proper ligand binds to the receptor, it triggers exocytosis, the release of the contents of the granules into the tissue. These cells are some of the major initiators of inflammation. The TLRs on the mast cells will trigger exocytosis when they interact with PAMPs, such as lipopolysaccharides, the endotoxins of gram-negative bacteria. Lipopolysaccharide is the endotoxin that is a normal part of the cell membrane on gram-negative bacteria. Another trigger for mast cells is the peptidoglycan of the gram-positive bacterial cell walls. Peptidoglycans react with receptors on immune cells.

Mast cells also have receptors for complement fragments that trigger exocytosis of their granules. C3a and C5a are the fragments that will trigger this reaction. Another trigger is bacteria coated with C3b fragments. Once mast cells are activated, they literally release dozens of their granules as inflammatory triggers. Some of these mediators are released immediately

from the granules, while others are released later as they interact and become activated.⁶

Some of these mediators work locally to create the signs of inflammation, while others act systematically to recruit more white blood cells from the immune system to help fight the invader. The latter include monocytes, local macrophages, neutrophils, dendritic cells, and all subclasses of lymphocytes. These lymphocytes include B cells, T cells, natural killer (NK) cells, and eosinophils. Recruited cells can become activated, help fight any infection that is present, and may produce their own mediators to increase the inflammatory process. If this process continues past the point of clearing pathogens, it can create cell damage and tissue destruction. One of the most prominent mediators of inflammation is tumor necrosis factor-alpha (TNF-alpha).⁷⁻⁹ TNF-alpha can quickly stimulate and turn on mast cells, which then release more TNF-alpha. When a cell is stimulated or activated by TNF-alpha through its receptors on all immune cells, it activates them quickly and they then produce large amounts of TNF-alpha, which continues the inflammatory reaction.

All immune cells involved in inflammation have receptors for TNF-alpha. This cytokine, an immune modulator, activates immune cells to produce their own cytokines and immune modulators. TNF-alpha can also induce cell differentiation and activation and lead to the progressive spread of inflammation. TNF-alpha is only one in the family of tumor necrosis factors; these can stimulate growth of cells, produce growth inhibition, or lead to cell self-destruction (apoptosis). Specifically, TNF-alpha can lead to tumor regression, septic shock, and cachexia, a wasting syndrome. Cachexia is characterized by anorexia, net catabolism, weight loss, and anemia. Another potent mediator and cell-activity modulator is cachectin, which is equivalent to TNF-alpha. Also a potent pyrogen, TNF-alpha stimulates fever, cell proliferation, and cell differentiation.^{1,10}

TNF-alpha is one of the prominent mediators seen in many and varied pathologic conditions that we presently deal with in medicine. It can induce septic shock and is one of the markers seen in cancer, AIDS,

transplantation rejection, multiple sclerosis, diabetes, rheumatoid arthritis, trauma, malaria, meningitis, ischemia-reperfusion injury (the loss of blood supply and oxygen and then the reestablishment of blood flow and oxygen), and adult respiratory distress syndrome.¹¹ TNF-alpha induces activation and neutrophilic division during inflammation; however, if it binds to TNF-R55 receptors, cell growth is not supported and can lead to cell death. The beginning of the reaction of TNF-alpha helps to promote remodeling and replacement of injured or senescence cells, but when it persists at high levels for an extended period of time, it loses its antitumor activity.^{10, 11}

TNF-alpha's ability to fight tumors is reduced for several possible reasons: It can be polymerized into chains of TNF-alpha, which are then inactive. The tumor cells can shed their TNF receptors or TNF-alpha can be broken down. Or an excessive amount of anti-TNF antibodies may be produced.¹¹

Tryptase is another active compound of inflammation. The most abundant protein released by mast cells, tryptase is a protease enzyme that activates C3 of the complement system. Through this activation, the complement fractions can activate more immune cells and attack any bacteria in the vicinity. It also functions as a chemotactic cytokine and attracts more leukocytes in the area.¹²

When activated in the local area of inflammation, macrophages and neutrophils start producing reactive oxygen species (ROS). These are toxic to microorganisms and can also lead to tissue damage and the propagation of chronic inflammation.^{13,14} Histamine is also contained in the granules of the mast cells and is a potent mediator released by exocytosis. Histamine works to increase blood flow to the area and causes leakage of fluid and proteins from the blood into the tissue space. The quick release and the reaction of the tissues to the histamine produce redness and swelling that is associated with inflammation.¹⁵

Interleukin-1 (IL-1) is found in the macrophages, monocytes, and activated platelets. This cytokine has local (paracrine) activity affecting

only the cells in the local vicinity and stimulates the production of tissue factors as well as helping to trigger blood clotting cascade. IL-1 also stimulates the synthesis and secretion of other interleukins. This process helps to activate T cells and thus initiates an adaptive immune response. Interleukin also has an endocrine or hormonal effect in that it is carried through the bloodstream to the whole body. This process can lead to a reduction in blood pressure and an increase in fever. The stimulation and release of prostaglandins affect the temperature control center of the hypothalamus, causing fever production.¹⁶

Bradykinin is a nano-peptide (a protein fragment composed of nine amino acids) which continuously circulates in the blood. Produced in the liver, it circulates in the inactive form of a precursor called kininogen. This is one of the molecules that makes up our alpha-globulins and is activated by a proteolytic cleavage of the precursor. Bradykinin acts to relax smooth muscle and the arterioles, thereby lowering blood pressure and increasing blood flow into the tissues. It also acts to make the capillaries leaky, which then allows more blood components into the tissue space, producing redness, warmth, and some of the swelling in the inflamed tissue. Bradykinin also stimulates the release of nitric oxide and the production and release of prostaglandins.^{17, 18}

Prostaglandins and leukotrienes are potent mediators of inflammation. Derived from arachidonic acid, they are unsaturated fatty acids produced from membrane phospholipids. Cyclooxygenase produces prostaglandin H₂ (PGH-2) or thromboxanes, and 5-lipoxygenase will produce leukotrienes.¹⁹ Both are powerful modulators of the inflammation process. They are active in both acute and chronic inflammation.

Acute inflammation is beneficial. It works to isolate the damage area and to mobilize protective cells and molecules to the site. This acute process works to promote the removal of damaged tissues and to increase healing. The problem occurs when the system does not work normally and those with infections have a greater difficulty in controlling them. This process is seen in chronic granulomatous disease and in people with inherited defects in producing some of the complement components. These individuals will

thus have greater risk of certain types of infections.¹

In the acute inflammatory process, the pathogens are either bacteria, viruses, or some dramatically injured tissues. The major cells involved are primarily neutrophils and some basophils. Eosinophils would be present if there were parasites or worms that were causing the infection. The primary mediators of the acute inflammatory process are monocytes and macrophages. The mediators (compounds) they produce are primarily vasoactive amines and eicosanoids. These create blood vessel dilation and leaking into the tissues. In this type of inflammation, the onset is immediate, and the typical duration will be a few days, leading to abscess formation. If not resolved, chronic inflammation is the result.

During the acute phase of inflammation, marked vascular changes occur where the vessels become more open, resulting in increased permeability through the walls and an increase in blood flow. The inflammatory mediator cytokines and other products previously discussed create these changes. The vasodilation begins in the capillary beds, increasing to larger and larger vessels, which helps to create the redness, heat, and swelling of inflammation. This increased permeability allows plasma to move into the other tissues with resultant stasis. As the blood vessels dilate, cells move from the center of the blood vessel to the periphery, along the walls. The endothelial cells of the vessel walls are coated with chemoattractants on their surface, and these cause the blood cells to move to the edges, slowing movement, and then to traverse the vessel cell wall between the endothelial cells.^{1,4,20,22}

These activities attract and direct cells into the inflamed tissues. The leukocytes in the bloodstream begin to slow and move to the margins of the blood vessels. As this occurs, they begin to roll slowly and then penetrate between the endothelial cells and move into the tissues. Known as the leukocyte adhesion cascade,²³ cells migrate into the tissue and the whole process of inflammation is carried out.

The resolution of inflammation is an active process. Inflammation needs to be ended when the inciting cause has been taken care of and there is no other tissue at the present time. When this process is working correctly,

neighboring tissue is not damaged and the inflammation is resolved. If this process does not end correctly, chronic inflammation and cellular destruction ensues.²² The different mechanisms for resolving inflammation will be determined by the type of tissue where the inflammation is taking place.^{22,24} One of the contributing factors to the resolution of inflammation is that the inflammatory mediators are decreased in the tissue. This is followed by a reduction in the macrophage activation and production and release of transforming growth factor-beta (TGF-beta), which comes from the macrophage itself.^{25,27} TGF-beta is produced with a reduction in the TNF-alpha production and a shift to TGF-beta.

If this process doesn't occur, and the macrophages continue to produce TNF-alpha, the inflammatory process will continue and expand. At other times, the production and release of interleukin-10 (IL-10)²⁸ functions to reduce inflammation. The production of anti-inflammatory lipoxins²⁹ can act as down regulators of the proinflammatory molecules such as leukotrenes. In addition, an up-regulation of anti-inflammatory molecules, such as Interleukin-1 receptor antagonists, or production of soluble tumor necrosis factor receptors can lead to the apoptosis of proinflammatory cells,³⁰ leading to the end of the inflammatory reaction.

If an inflammatory reaction progresses for an extended period of time, some receptors are desensitized. An increase in inflammatory cells in the inflamed area will lead to a continued interaction with the extracellular matrix (ECM);^{31,32} with the increase in cells and ligands, the receptors reach a point of saturation and they then begin to down-regulate. There can also be cleavage of some chemokines by the matrix metalloproteinases (MMPs) and the subsequent production of anti-inflammatory factors.³³

In the case of chronic inflammation, the inflammatory process rages out of proportion to the threat, or it may be directed against inappropriate targets. This can lead to more damage to the body and be even greater than the threat from the triggering agent itself. All allergies and many autoimmune diseases are examples of this type of reaction. The formation

of antibodies against “self” or persistent antigens from a smoldering infection can, in some cases, make the problem worse. In these cases, a formation of antibody complexes act to trigger the complement system and create more mediators of inflammation.¹

Persistent acute inflammation, nondegradable pathogens, viral infections, persistent foreign bodies, or an autoimmune reaction can result in chronic inflammation. The cells involved tend to be mononuclear cells, such as monocytes, macrophages, lymphocytes, plasma cells and fibroblasts. In chronic inflammation, some of the primary mediators are interferon gamma (IFN-gamma), cytokines, growth factors, ROS, and hydrolytic enzymes. This whole process is delayed and may last up to months or years, creating tissue destruction fibrosis and necrosis.²²

As one begins to understand the complexity of the process and resolution of inflammation, it becomes increasingly clear that there must be things we can do to prevent this process from even starting and continuing. At the core of everything we do to maintain our health is diet. We can eat things that are pro-inflammatory, or we can eat things that help reduce inflammation. We can take supplements, for example, that will help to prevent and control chronic inflammation. The current American diet is filled with processed food and genetically modified food and is, overall, very acidic. Processed oils tend to increase the process of inflammation, as well as fatty meats and dairy, foods with trans-fats, sugars and other sweeteners, and flour containing genetically modified gluten. The simple-carbohydrate foods also contribute to inflammation, including white rice, as do omega-6 oils, some peppers, tomatoes, and eggplant. These can all contribute to increase and propel inflammation.³⁴

Rather than avoiding all of these foods, we need to choose foods that are alkaline and provide our body with what it needs to control inflammation. Spices such as turmeric or curcumin help to control inflammation. Complex carbohydrates, such as fruits and vegetables, are more beneficial for our body than simple carbohydrates. Lacto-fermented foods, such as pickles and beet kvass, provide us with probiotics, digestive enzymes, vitamins, and minerals. These foods, along with natural supplements, help

us to control inflammation.

As we look at diet in our lives, we can draw one conclusion: The commonality between all of our chronic diseases is inflammation, and inflammation itself is a link to our diet. Our diet, therefore, is one of the first things that we need to change.

The plant *Cannabis sativa*, as described in chapter 1, is one of the oldest and most studied of the natural substances. It provides phytocannabinoids, some of which contain antioxidants, are anti-inflammatory and neuroprotective, and can help us to control chronic inflammation. Cannabidiol (CBD) is one of the phytocannabinoids, an antioxidant that acts as an immune modulator, is anti-inflammatory and protects mitochondria from damage. Nonpsychoactive, CBD is used to help control seizures and antitumor activity and can turn off genes for the metastasis of some tumors.

In this book we look at many of CBD's applications and the methods by which anyone can accomplish these goals for health. *Cannabis sativa* is a natural herb. It grows on this earth for our benefit. Hopefully, we as a society will begin to look at it again, to understand how to use it for our benefit. It has the potential to benefit anyone who has chronic inflammation. CBD can aid and assist in reducing inflammation and protecting the cells that surround the area of inflammation in any system, organ, or tissue. Since most diseases are associated with chronic inflammation, using CBD enables us to intervene to reduce the inflammation and protect the neighboring undamaged cells.

III

The Endocannabinoid System

The endocannabinoid system is designed to maintain homeostasis balance in our bodies.¹ It interconnects all systems, organs, and tissues and responds to changes in the internal and external environment. Its whole purpose is to keep our bodies functioning at their best by adapting to change. When the endocannabinoid system is working correctly, we are in balance and function at our maximum potential. When this system is underresponding or overresponding, we begin to have physical and mental issues.

The endocannabinoid system is based on lipid mediators⁷³ that are metabolized on an as-needed basis. The compounds are quickly made and broken down. Their function is to help us respond to stress by modulating the endocrine system's response to environmental changes. They also help us to modulate inflammation in the body and to regulate our fight-or-flight response.

The trigger for learning about cannabinoids came from the experiences with phytocannabinoids, cannabinoids that are derived from plants. Of particular interest was the action of delta-9-THC from the marijuana plant. As they speculated on how THC produced its psychotropic effects, chemists began to look at the plant and discovered more than 60 cannabinoids. Research continues on the effects of each of these phytocannabinoids on our body.

In 1963 the structure of CBD was discovered,² followed in 1964 with the discovery of the structure of the psycho-active compound in marijuana. It

was first called delta-1-tetrahydrocannabinol and the nomenclature was later changed to delta-9-THC.³ From this research it became evident that our cells had some way to interact and respond to the cannabinoids. In 1988 a cannabinoid receptor was discovered in the rat brain.⁴ The receptors were part of the Gi/o family of G-protein coupled receptors and similar to many other receptors in our body. These receptors help modulate ion channels, the calcium and potassium channels that move these ions in and out of cells. These channels help modulate neurotransmission.¹² Many hormones act through G-protein coupled receptors.¹¹

In 1990 the cannabinoid receptor type 1 (CB1) was cloned.⁵ This receptor was found expressed in the central nervous system (CNS) and other tissues and organs in the body. There are a few CB1 receptors in the medulla oblongata, so they do not regulate respiration and cardiovascular function. This precludes a reaction of respiratory failure or cardiovascular collapse from marijuana consumption.¹¹ The receptors were also found in the cardiovascular system, the reproductive system in both males and females,¹¹ and the gastrointestinal tract.¹³ It was discovered that this CB1 receptor is responsible for the psycho-trophic activity of delta-9-THC.

A high density of CB1 receptors exists in the basal ganglia, especially the globus pallidus, which helps control unconscious muscle movements, and planning and starting a movement.¹⁴⁻¹⁶ A high concentration also exists in the limbic system. In the amygdala, these receptors influence emotion, such as fear and anxiety, and this is paired with a high number of CB1 receptors in the hippocampus, which is involved in learning new information and memory integration.¹⁴⁻¹⁶ In the cerebellum, these receptors affect motor coordination and balance. In the brain stem they affect the transmission of information from the brain to the spinal column and the spinal column to the brain. This area also helps control nausea. The cannabinoid receptors in the hypothalamus help modulate eating and sexual behavior. Those in the neocortex and forebrain support complex

thinking and higher cognitive function, feeling, and movement.¹⁵ The cannabinoid receptors in the nucleus accumbens modulate motivation and reward. Some of the cannabinoid receptors in the spinal cord regulate the transmission between the body and the brain, modulating pain sensitivity and perception.

The CB1 receptors are located presynaptically, and the endocannabinoids are made in response to the neuron firing. They are made in the postsynaptic membrane and then move in a retrograde manner to affect the firing of the presynaptic membrane. They will help modulate what neurotransmitter is released and how quickly the neuron can fire.^{31,39,40} The CB1 receptors are associated with special microdomains called lipid rafts. These lipid rafts respond to changes in cholesterol levels. With increased cholesterol levels, they reduce binding to the CB1 receptors. They also help modulate endocannabinoid signaling.⁸⁶⁻⁸⁸

In 1992 the first endocannabinoid was discovered⁶ and named anandamide, meaning “internal bliss.” The chemical name was N-arachidonoyl ethanolamide (AEA). The next step in discovery was identifying receptors for cannabinoids and the presence of the first endocannabinoid. Anandamide is a modified form of arachidonic acid, a compound synthesized by the enzyme N-acylphosphatidylethanolamine-specific phospholipase D (NAPE-PLD).⁷⁵⁻⁷⁶ The structure of this compound is different from THC and functions in both the central and peripheral nervous systems. There is a cross-tolerance to THC;¹⁹ both THC and anandamide increase the affinity and number of cerebellar and hippocampal receptors after acute and chronic use.²⁰ Both of these compounds are strong CB1 receptor agonists and weak CB2 receptor agonists. After its use, the anandamide is degraded by fatty acid amide hydrolase (FAAH), breaking it down to arachidonic acid and ethanolamide. FAAH is the enzyme that degrades some of our endocannabinoids. Anandamide acting at CB1 receptors provides neuromodulatory function. Unlike other neuromodulatory molecules, it is

produced in the postsynaptic membranes in response to its firing. Nerve impulses move from the presynaptic membrane across the synaptic cleft to stimulate the post-synaptic membrane. When this occurs, anandamide is produced and moves in the reverse direction from the post-synaptic membrane to the CB receptor on the presynaptic membrane. This interaction modulates the Ca²⁺ and K⁺ ion movement and stimulates adenylyl cyclase activity. Through this activity, it modulates the neurotransmitter release.⁸⁴

The discovery of anandamide was followed in 1993 with the cloning of a second type of cannabinoid receptor, endocannabinoid receptor 2 (CB2).⁷ This receptor was found in peripheral tissues and organs, principally in immune system cells, and a second isoform was later found to be present and active in the CNS central nervous system.¹⁰ The CB2A isoform has higher concentration in the testis and the brain, while the CB2B has a higher expression in the peripheral tissues.^{10h}

The CB2 receptors were found in the cerebral cortex in the orbital, visual, motor, and auditory areas. They were also found in the hippocampus, both CA2 and CA3 areas, the corpus collosum, cerebellum, brain stem, and pineal gland.¹⁰ Peripherally they were found in the marginal zone of the spleen,¹¹ in the immune system, in the lymphocytes, macrophages, NK cells, and other immunocytes.¹⁷ From this distribution the CB2 receptors can modify brain function and immune function. CB2 receptors were also found in the enteric nervous system, which helps modulate gastrointestinal contractility.¹⁸

In 1995 a second endocannabinoid was discovered and named 2-arachidonoyl glycerol (2-AG). 2-AG is more CB2 receptor-selective, as it will bind to both CB1 and CB2 receptors.^{8,9} It is produced more in peripheral tissues and was first discovered in canine tissues.²¹ It is also derived from arachidonic acid and is synthesized by a phospholipase C compound—sn-1-diacylglycerol lipase (DAGL)⁷⁷ and is broken down by monoacylglycerol lipase (MAGL).⁷⁸ It has a similar activity to THC in

peripheral tissues. Several other endocannabinoids have been described, including palmitoyl-ethanolamide (PEA), docosatetraenylethanolamide (DEA), homo-gamma-linolenylethanolamide (HEA), virodhamine, noland ether, oleamide, and oleoylethanolamine (OEA).⁷³ All of these compounds are a family originating from arachidonic acid and are unsaturated fatty acid ethanolamides that bind to cannabinoid receptors. They can all produce behavioral effects, pain perception modification, learning, memory, and sleep. The activities of the endocannabinoids and phytocannabinoids are not limited to only cannabinoid receptors.

With the discovery of the receptors, it became obvious that we had an endogenous system with receptors and active compounds. The distribution of the receptors indicated that these compounds helped with the modulation of neuropeptides and hormones, and that, through these interactions, the endocannabinoid system helped modulate the regulation of the brain and behavior.^{93,96} All of this information came from the study of the herb marijuana and, with it, the discovery of a complete system that functions to help us stay in balance. The endocannabinoid system affects all systems, organs, and tissues, so when it is out of balance, we are out of balance and disease develops. The illnesses can be from too little or too much cannabinoid tone (the baseline amounts of endocannabinoids produced). Most people have not had their cannabinoid system supplemented since they were breast-fed. If they were not breast-fed, this system has not been supported since birth.

IV

Anxiety

Anxiety is the most common diagnosis given today, so prevalent that its treatment now supports multiple medications. Anxiety is a complicated physiological process, and, through experimentation, we have learned much about which parts of the brain are active in anxiety. Anxiety is different for each person experiencing it. It can be perceptual in that some things that produce anxiety for one person may not create it for someone else. Anxiety is dependent on a person's interpretation of another person, place, or event. Something that seems perfectly normal to one person might appear to be threatening and overwhelming to another. Complicating factors for anxiety are those instances that might not be an event that is actually happening but rather anticipation or worry about possible events or even an inward interpretation of an event that is happening. These are reflections of our individuality, and their complexity is important to understand.

Anxiety has specific triggers, and, as these triggers are processed, they can be generalized and create even more triggers. This can happen with thoughts that create anxiety, and the thoughts then become obsessive and repetitive. I believe the obsessive complex begins to develop to help reduce anxiety. For many children on the autistic spectrum, for example, the obsessive-compulsive activities start from a core of anxiety or fear.

Recurrent thoughts or repetitive activities help some people reduce the level of anxiety or fear. They provide a method of coping with the anxiety or fear by giving them something they can control. This brings to mind the whole flight-or-fight mechanism. When fearful or anxious emotions are

present, our body is in a constant state of readiness to either fight or run. Cortisol levels are elevated, the heart rate increases, breathing is rapid and shallow, and the body becomes dependent on the subsequent adrenaline rush. If this dependency is developed, then there is gravitation toward similar situations that create the same feeling. Situations are modified to become fulfilling.

The whole cycle may become self-reinforcing and repetitive, and from this long-term place of constant elevated stress reaction, the body's overall function is unbalanced. Anxiety shuts down the frontal cortex, leading to reduced memory and reduced executive functions. It's not difficult to understand that anxiety makes it difficult to cope and successfully thrive in our society. In everyday life, we need to be remembering and processing nearly constantly, and none of these functions are maximal when we are experiencing anxiety. The greater the anxiety, the less we are able to function, and our ability to function from moment to moment is decreased. By just living life, we are then creating more and more triggers for more anxiety. When this occurs in early life, education is severely affected, not just in the classroom but in social education as well. When widespread, this anxiety can make even leaving the house intolerable.

Triggers for anxiety are personal, so understanding their origin or starting place is difficult. Since the triggers in the whole process are individualized, we must approach each person differently and use personalized therapeutic interventions. When developing a treatment plan, one must understand the areas of the brain involved and the balance of the neurotransmitters. One must begin with underlying support of the natural processes that help reduce anxiety.

Our microbiota has a tremendous influence on how we react to stress and therefore influence anxiety. This appears to be a starting place as microbiota accounts for 80 percent of our innate immune system. Our microbiota helps produce our neurotransmitters, serotonin, and dopamine. Our microbiota also helps influence our hypothalamic pituitary adrenal (HPA) axis in its response to stress. The connection between our gut and brain is a powerful one, and microbiology even influences calm and aggressive behaviors. We must approach anxiety from the basis of the

microbiota and its influence on the body.

Our body works as a whole and not in isolated segments or sections. Understanding this and understanding multiple interactions enables us to further hone the approach to working with anxiety. To calm the anxiety, we basically must start from the ground and work our way up. We cannot expect to just treat symptoms and have anxiety go away. The approach must include looking for those pieces that are out of balance, moving from the basic to the more complex. This is where CBD can be of great value.

CBD helps to calm anxiety by working in different parts of the brain where the anxiety starts and helping one to release triggers. This is accomplished with low doses; when doses get too high, anxiety may increase. When treating anxiety with CBD, we start with the basics and move up. When started at low doses and gradually worked up, CBD has no psychotropic effects. If large doses are given at the start, CBD can block the reuptake and degradation of our own CB1 receptor agonist, anandamide, and cause a feeling of spaciness. Nonetheless, the safety profile of CBD is extraordinary, and, with proper use, it can be very effective in treating anxiety in young people without creating any problems. Since there are no cannabinoid receptors in the respiratory and cardiovascular nuclei in the brain stem, death is not a risk in taking cannabinoids. The biggest side effects are “the munchies” and sleepiness.

The limbic system functions in disorders related to anxiety and stress,¹ helping to mediate emotional learning^{2,8-15} and affecting and interacting with the complete neurophysiological system of stress, anxiety, and fear.¹ The endocannabinoid system helps us to modulate our stress reactions and is heavily expressed in brain areas associated with stress, fear, emotion, and reward, such as the amygdala, the nucleus accumbens (NAc), the hippocampus, and the prefrontal cortex (PFC).³⁻⁷

Stress is defined as any situation that challenges the homeostasis of the organism and may be perceived as actual or potential changes in the individual's environment. These may be real or perceived,¹⁸ and a dynamic endocannabinoid system helps regulate or modulate the HPA axis system. The endocannabinoid system thus helps regulate a stress

response, anxiety, and the extinction of fear learning.^{8, 19, 20} Fear is an adaptive component of the acute stress response or reaction when we are faced with potentially dangerous situations or environments.¹ When fear is disproportionate in intensity or chronicity, is irreversible, or is not associated with any actual risk, then it is considered maladaptive and can lead to anxiety-related psychiatric disorders.²⁰ The brain regions involved in stress, anxiety, and posttraumatic stress disorder (PTSD) include the amygdala, the prefrontal cortex, and the hippocampus.²¹

The hippocampus contains large numbers of both mineralocorticoid and glucocorticoid receptors.²² Stress-induced corticosteroids signaling in the hippocampus have a beneficial role in regulating the time course of the HPA axis stress response,²² but prolonged glucocorticoid signaling can damage the hippocampus, causing dendritic atrophy, decreased neurogenesis, and deficits in synaptic plasticity.²³⁻²⁶ In PTSD and major depressive disorder, patients' hippocampal volumes are reduced,²⁷⁻²⁹ and smaller hippocampal volumes are predictive of vulnerability to the development of stress-related disorders and depression.³⁰

The amygdala has a central role in the control of emotions and autonomic responses to stress, mood regulation, and mediation of fear and stress responses.^{31,32} There is a bidirectional relationship with the frontal cortex³³ and hippocampus.³⁴ Each has influence on the other, both in forming and releasing stress responses. The human amygdala is responsive to a multitude of salient stimuli, such as fear conditioning, emotional stimuli, and facial expressions. However, it responds reliably and potentially preferably to stimuli that project threat and can be involved in mediating fear and anxiety states.

The experience of fear as a “distress response” to possible predictors of threat is present in anxiety disorders. The amygdala is hypothesized to be hyperresponsive in some stress reactions. A reaction follows that may create hyperresponsive reaction in some anxiety disorders. Scientists have proposed that the amygdala is hyperresponsive in PTSD and that it's this

hyperresponsiveness that accounts for the exaggerated response to, and persistence of, traumatic memories.²¹

The prefrontal cortex has an integral role in mediating a range of executive functions that subserve the selection and processing of information necessary to plan, control, and direct behavior in a manner appropriate to the current environmental demands.³⁵⁻⁴⁰ This is an area where an imbalance in the endocannabinoid system will show in many inappropriate or disproportionate reactions to some situations. The prefrontal cortex plays a major role in orchestrating behavioral and systemic responses to stress. Neurons of the prefrontal cortex in rats have extensive remodeling in response to stress. Stress-induced alterations in the prefrontal cortex function represent the principal neural insult from stress and lead to deficits in executive function in rodents and to many neuropsychiatric diseases⁴¹ in humans. In addition, the amygdala and hippocampus establish roles in encoding and processing memory for emotional stressful events into long-term storage.⁴²⁻⁴⁹

The NAc is involved in mediating stress-related dysfunction.⁵⁰⁻⁵² The shell of the NAc has an important role in integrating and consolidating representations of new experiences that are initially processed by both the amygdala and hippocampus.⁵³⁻⁵⁵ The shell of the NAc receives neural input from the basal lateral amygdala concerning the effective components of the experiences^{56,57} and is the “emotional” content of the new experiences.

Projections from the hippocampus, ventral subiculum region, convey information about the context of events occurring in the environment, along with reward-related components of learning experiences from the ventral tegmental area. Contextual features would look at permanence, transient features, relevance to the whole situation, and whether this has a possibility of recurrence.⁶⁰ The interconnecting of multiple areas allows the endocannabinoid system to modulate unconditioned stress- and anxiety-like responses.^{8,11,13} Inhibition of the interconnecting signaling increases stress and anxiety, and moderate increases in the signaling

decreases stress and anxiety.¹³ High increases in CB1 receptor stimulation will increase stress and anxiety-like responses.^{13,61,62} Endocannabinoids have a biphasic response; low doses are anxiolytic and high doses can be anxiogenic.^{14,63} Low doses reduce anxiety and stress, while moderate to high doses increase anxiety and stress responses.

Cannabis may induce aversive states in some people, and even anxiety or panic attacks.⁶⁴ The administration of THC may result in psychotic-like states.⁶⁵ With the biphasic effect, low doses of CB1 receptor agonist are helping to release the triggers, while high doses can increase aversion and anxiety-related behaviors.⁸ At higher doses, the CB1 receptor agonists begin to stimulate transient receptor potential vanilloid type 1 (TRPV1).⁶⁶ This may participate in the negative effects of higher doses. CBD also stimulates TRPV2 receptors, located on afferent nociceptors. This means that they participate in the transduction of chemical, thermal, and mechanical stimuli. The TRPV1 receptors are located in the hypothalamus, cerebellum, hippocampus and frontal cortex, and play a significant role in inflammation and neurodegeneration.¹⁰⁰ They also play a role in the modulation of the limbic emotional response to fear and anxiety. TRPV2 receptors contribute to ionized calcium (Ca^{2+}) influx, modulate sensitivity for cytotoxic compounds, and help to regulate apoptosis.⁹⁸⁻¹⁰⁰

Anandamide is our normal and natural CB1 receptor agonist; an increased concentration of anandamide will affect not only the CB1 receptors but also begin to affect the TRPV1 receptors. Part of the action of CBD is to block the reuptake and breakdown of anandamide. This is part of the reason that CBD has a biphasic response, reducing anxiety at low levels and increasing anxiety at high levels. Due to the increase in anandamide and its effect on CB1 receptors, CBD can assist in PTSD therapy by helping to release the triggering memories.

The action of CBD is partially related to its ability to reduce the enzyme FAAH, and it further acts by blocking the reuptake protein that removes anandamide from the receptors.⁶⁷ Anxiety disorders, including PTSD and

phobias, are the result of dysregulation of the neural circuitry controlled by the endocannabinoid system.⁶⁸ This imbalance can be improved and reversed by the use of phytocannabinoids and, in particular, CBD.

Using conditioned fear in animals has been a way to understand the mechanism by which aversive memories are formed^{1,68} and then understanding the basis for PTSD and specific phobias. By blocking CB1 receptor activity or antagonizing CB1 receptors, we see an increase in the acquisition and expression of “cue” fear conditioning.^{69,70} When CB1 receptors are antagonized in the basolateral amygdala, the fear response and conditioning increases, demonstrating that the “cue” fear conditioning depends on the amygdala and not the hippocampus.^{12, 71} Blocking or inhibiting the endocannabinoid systems increases fear; moderate stimulation will decrease fear.¹

An inability to extinguish memories of fear is at the root of all fear disorders, including panic attacks, phobias, and PTSD.⁷²⁻⁷⁴ Extinction learning involves the ventromedial prefrontal cortex, amygdala, and hippocampus.^{47,75,76} The lack of CB1 receptor stimuli allows acquisition and consolidation of fear conditioning and also impairs fear extinction.^{2,63,77-81} Given this complexity, an individual may need more or less CB1 receptor activity, requiring a combination of CBD and THC in different percentages or ratios.

The activation of the cannabinoid CB1 receptor promotes extinction of our fear memories.⁷⁵ The inhibition of FAAH enhances the rate of extinction⁸² by increasing the amount of anandamide and activity at CB1 receptors, which is accomplished with CBD. Anxiety responses and fear learning are affected by the endocannabinoid system. This system acts on the amygdala in the lateral basal nuclei, which has high concentrations of CB1 receptors.⁸³ For these reasons, CBD activity is complicated. It is a weak CB1 receptor antagonist, but at the same time it blocks the activity of FAAH and thereby increases anandamide, which is a CB1 receptor agonist. These pieces point to the need for knowing or appreciating the

individuality of the possible responses.

Extinction of aversive memories depends on cannabinoid receptors and signaling within the basal lateral amygdala, which then goes to the prefrontal cortex.^{2,9,84} The activation of CB1 receptors decreases anxiety responses and amygdala activation to aversive stimuli by modulating the cannabinoid firing in the basal lateral amygdala.^{85,86} Acute stress enhances the conditioned avoidance and impairs inhibitory avoidance extension.¹² This reflects a balance that must be maintained, because too much stimulation on either side can create issues with anxiety and fear. With the cannabinoid stimulation, we can prevent stress-induced conditioned avoidance and reduce the retention of the important trigger event. CB1 activity in basal lateral amygdala also contributes to alterations in the HPA axis.¹²

The HPA activation, through CB1 receptors, reduces the production and release of corticosteroid production and modulates both basal HPA axis activity and fine tuning of a stress response.⁸⁷ HPA axis response to stress is the acute release of corticotropin releasing factor (CRF), released into the portal system by neurons in the periventricular nucleus (PVN). The corticotropin releasing factor induces the release of adrenocorticotrophic hormone (ACTH) from the pituitary. ACTH stimulates the production of glucocorticoids (corticosterone in rats or cortisol in humans) in the adrenal gland. The glucocorticoids have a wide range of effects on the cardiovascular system, the immune system, the metabolic system, and the neural systems, which in turn induces the optimal response to a personal stimulus, as multiple people can be in the same environment and each have their own personal experience or interpretation of the events which occurred.⁸⁸ This is the basis of the fight-or-flight response. In an acute situation, this can be protective; however, on a long-term basis, this is destructive, causing more problems than it solves.

Cortisone also exerts negative feedback for the HPA axis, inhibiting the further release of CRF and ACTH from the axis. The amygdala activates

the HPA axis,^{1, 88} while the hippocampus and prefrontal cortex inhibit it^{1,88} Stressful events cause an increase in the endocannabinoid stimulation in several brain areas in response to the stimulation of glucocorticoid receptors.^{89,90} Stress stimulates and increases endocannabinoid production in the periaqueductal gray matter in the midbrain.⁹¹ Stress causes changes in the endocannabinoid system in the limbic forebrain, the amygdala, stratum, and in the prefrontal cortex.^{86,92}

CBD blocks transporter protein for anandamide, blocks FAAH breakdown of anandamide, or both, which in turn reduces corticosteroid release in stress-induced reactions⁹³. This increase in anandamide is accompanied by the administration of CBD. This also reduces activation of the HPA axis and the cannabinoids' negative modulation of the axis. Stress itself induces a reduction in the endogenous anandamide present in the amygdala through an increase in FAAH activity.^{86,92,94} This is one of the places where CBD can help to control the stress response.

CB1 receptor agonists have a biphasic activity with regard to anxiety-like behaviors in the HPA axis activation. Low doses reduce anxiety and reduce corticosteroid release. The endocannabinoid system is an important regulator of the central stress response, and alterations of the cannabinoids help reduce stress responses and prevent stress-related diseases.

CB1 receptor agonists also reduce gamma-aminobutyric acid (GABA) in the basal lateral amygdala interneurons, reducing inhibition of the GABAergic neurons in the intercolated nuclei. This increases their inhibition of the parental neurons in the central amygdala.⁸³ Reduction in this inhibitory tone may indirectly reduce anxiety by increasing the activity of the hippocampus and forebrain and inhibit the activation of the central amygdala.⁸³

Cannabinoids decrease CRH levels in the central amygdala, which is associated with decreases in aversive stress responses.⁶¹ There may also be interactions with other neurochemicals, such as serotonin, cholecystinin, and opioids.⁹⁵ Moderate stress, learning, extension of the

fear, and emotional learning reward processes are associated with functions of the amygdala and hippocampus NAc and the prefrontal cortex.⁹⁶ Stimulation of these areas causes a reduction in anxiety and some antidepressant activity.^{66,97-99} CB1 receptors are required for neuronal emotional learning and memory,⁹ and are essential for the extinction of conditioned fear.¹⁰⁰ The blocking of CB1 receptors completely blocks emotional learning.

CBD's action is not through the cannabinoids receptors. CBD is a reverse agonist of CB1 receptors and is a weak agonist. Part of its effectiveness against anxiety is through its ability to block FAAH in the protein reuptake for anandamide. Anandamide is our natural CB1 receptor agonist. Through modulation, we get either increase or decrease anxiety. With the biphasic activity, we must remember that, at higher doses, we will increase anxiety rather than reduce it.

This activity is mainly seen in the amygdala, hippocampus, and prefrontal cortex. CBD has benefits other than just calming anxiety. The help with releasing triggers has been shown to have some benefit with PTSD. Through modulation, CBD is a very effective anxiolytic with no psychotropic effects. With the proper therapy and use of low doses of CBD, traumatic memories are released and normal function can return. Understanding that CBD is just one of many cannabinoids, we can surmise that research will show that combinations of cannabinoids will give us greater benefits than any one by itself.

Many additional valuable and holistic approaches and therapies can be used to calm anxiety. One of the best resources for these is a book called *Freedom from Anxiety* by Marcie Shapiro.

V

Immune System

Our immune system is complex and serves us in many capacities. It protects us from invasion from the outside by microorganisms and, on the inside, by clearing out damaged cells. It is balanced between two sides, the Th1 and the Th2. The activity it carries out shifts between them, with the Th1 as the clearing, antiviral and anticancer side, and the Th2 the antibody-producing side.

This system has to be in balance and able to shift back and forth, like a teeter-totter: when one side is active, the other side is suppressed. If the system becomes locked into one side, the other side does not function. The shifts can be caused by recurrent infections, heavy metals, or genetic predispositions. A look into the diseases reveals that chronic inflammation is at the base of the problem.

Chronic inflammation sets up a chronic shift in the immune system. This shift is on the Th1 side, where the promotion of cytokines produced at the site of inflammation are preventing the immune response from shifting. When this occurs in a particular area, the cells become damaged, more immune cells are called into the area. The immune cells become activated and start producing more inflammatory cytokines, which continue the immune response. If the response continues to escalate, the damaged cells are not removed or repaired but the damage begins to spread and affect the surrounding cells.

The triggers for this process are varied and multiple. Looking at the diseases reviewed in this chapter, we can see that each type has its own specific trigger or cause. In the big picture, it comes down to the question

of whether someone suffering from one of these diseases can help remediate the problem and modulate the immune system. To help modulate the immune system, the patient has to be able to turn off the inflammatory promoting cytokines. The cytokines are the controllers of immune system function. These compounds travel through the blood stream and function throughout the whole body. When inflammation is established in one area, the whole body knows and begins to respond.

Interferon and multiple cytokines, chemokines, and interleukins have specific functions. Some recruit more immune cells, some provide a trail for immune cells to follow, and some activate new recruited immune cells. Each immune cell has its own function and when a cell becomes activated, it will begin to provide its particular abilities to the area where it has been summoned. Some will attack, ingest, and destroy a bacteria or a virus. Others will present the markers of the invader and then present these to other immune cells that can produce antibodies. Still other immune-system cells will attack and destroy cells that have viruses or microbes in them. These cells will also attack cancer cells.

In autoimmune and neuroinflammatory disease, there is a Th1 shift. This shift is maintained and escalated by repeated and persistent presence of Th1 cytokines, chemokines, and interleukins. As long as these are present, the process is reinforcing and expanding. It must be broken by a modification in cell activation and reduction, or a change in the cytokine and interleukin profile. The common stimulators of this Th1 side include interferon-gamma, interleukin-2 (IL-2), TNF-alpha, and lymphotoxin. When these are continually made, the inflammatory process will continue and inflammation will spread and result in tissue damage from cell destruction.

This is the process that is seen in autoimmune and neuroinflammatory diseases. Control over these cytokines and interleukins can mean the progression or the cessation of the disease. When one looks at the activity of phytocannabinoids, it is obvious that they can be helpful in controlling the Th1 shift and begin to give support to end the Th1 cycle of destruction. CBD has been shown to reduce the production and release of TNF-alpha from arthritic synovial cells.² Part of the decrease in the production of

TNF-alpha came from the stimulation of adenosine A2A receptors.³ CBD has also been shown to reduce the production of interleukin-8 (IL-8) and other chemokines, thereby suppressing human B cell activities.^{2,62,63}

CBD has also been shown to reduce the release of ROS, demonstrated in zymosin-stimulating neutrophils.² It was also demonstrated that CBD can reduce nitric oxide production in macrophages.² All of these activities are helping to reduce oxidative stress and immune imbalance. The cannabinoids have also been shown to reduce the production of interleukin 10 (IL-10) through the cannabinoid receptors, seen in both macrophages and splenocytes.² The capabilities of cannabinoids can help reduce all of the proinflammatory cytokines, interleukins, chemokines, and interferon that support a Th1 shift.²⁻⁸

A wide distribution of CB2 receptors exists in immune cells.¹⁰⁻¹⁵ CBD has been shown to block the production of antigen-specific antibodies and can suppress T cell proliferation and the production of interleukin-2, interleukin-4 and interferon-gamma.^{2,5-7} CBD can also induce cell death in immature immortalized T-cells, an activity produced by the generation of ROS within these cells. CBD has been shown to be effective in the modulation of immune reactions within the central nervous system (CNS). The CB2 receptors are increased in microglial cells when inflammation is present, therefore providing a good opportunity to reduce inflammatory reactions and activation.

It has been shown that the CB2 receptors play a role in B-cell differentiation.¹⁷ These are the cells that produce antibodies. When they are suppressed, the body is more open to some types of infections, including *Legionella pneumophila*, *Staphylococcus albus*, *Treponema pallidum*, Friend leukemia virus, and *Acanthamoeba* (a protozoa genus).^{28,32-36} It has been shown that agonists of the CB2 receptors can suppress the proliferation of both B and T lymphocytes.³⁷⁻⁴⁰ They can also suppress the activity of NK cells,³⁹ which are the cells that lead to cell destruction and the proliferation of autoimmune diseases or neural

inflammation.³⁹ These compounds have also been shown to reduce the ability of cells to move toward the site of inflammation, therefore reducing immune cell recruitment and limiting injury.^{41,42}

The application of exogenous or phytocannabinoids shifts the immune profile from proinflammatory Th1 to two or more antiinflammatory Th2 stances.^{17,43-46} Observing the activity that these compounds produce leads to an understanding of the tremendous benefit they provide in helping to control autoimmune disease and neuroinflammation.⁴⁷⁻⁵⁷ They have the capability of turning off the attack by the immune cells, helping to reduce some of the oxidative stress, and supporting and protecting the normal cells.⁵⁸⁻⁶⁷

Understanding the effects of the cannabinoids and cannabinoid agonists leads us to conclude that we have an opportunity for control of diseases for which we have not previously had influence.⁶⁸⁻⁷⁹ However, we must be cautious and not push the Th2 side of the immune system too far and stimulate the production of more allergic-type diseases.⁸⁰⁻⁸⁴ As with anything, balance and caution is needed and important. The use of these compounds must be followed by looking at CD lymphocyte subsets and monitoring the Th status of the individual.⁸⁵⁻⁸⁸

VI

Seizures

The seizures are complex, with many types and causes. Types include partial seizures, absence seizures, and generalized seizures. Many illnesses—as well as toxic exposures, meningitis, and other infections of the CNS—can cause seizures. Sometimes we know the cause of the seizure, but often we don't. From the perspective of knowing the side effects of current epilepsy medications, and the fact that many seizures are not controlled by them, we look further for other compounds that help us to modulate the seizures. This is where CBD can play an important role. Many patients are helped by CBD alone while others need a combination of CBD and THC. The goal of the physician is to find the exact support that each patient's body needs to help reduce and even stop the seizure activity.

When a patient presents with seizures, doctors need to ask a lot of questions. They need to know when seizures started, how long they last, and what type of seizure the person is experiencing. Seizure activity is influenced by neurotransmitter abnormalities, so understanding these and striving for balance is important. Another issue that can contribute to seizure activity is liver function. If the liver is not working normally and removing toxins, they can build and cause irritation in the brain, leading to seizures. Supporting detoxification is very important. Another basic piece to understanding and treating seizures is supporting and balancing the microbiome. Dysbiosis (an internal microbial imbalance), with the reduction of normal flora and an increase in pathogenic bacteria, can cause or contribute to seizures. We depend on our normal microbiome to help balance the activity and responses of our hypothalamus, pituitary, and

adrenal gland. The microbiome also helps to modulate the immune system, another important factor in seizure activity and control. The microbiome provides 80 percent of our innate immune response; the microbes in it are our first responders to the introduction of pathogens. They tell us how the immune system is working, whether there is a Th1 or Th2 shift, or whether the immune system is in neutral and not contributing at all. When the immune system is out of balance, inflammation and seizure activity can be ongoing. Knowing a patient's infectious-disease history is essential to understanding the patient's seizure activity, because bacteria, viruses, and fungi can cause or exacerbate seizure activity, either during or after the infection.

A patient's vaccination history is another important component of understanding seizures. Because of the adjuvants and other compounds in vaccines, vaccines can trigger seizure activity. Heavy metals are toxic to the brain and can affect cellular activity and cause energetic imbalances in the mitochondria. These issues in the mitochondria in turn can contribute to seizure activity. Hydration and mineral status are also very important determinants as these, too, can contribute to seizures. One of the most impressive seizures that I've seen was precipitated by dairy and gluten in the diet. When these proteins are not digested normally, they become neuroactive peptides, which can interfere with neurotransmitter function and interact with opiate receptors and overall brain function.

We are exposed to many toxins in our environment each day and can support our body's detoxification system by helping it to remove toxins. General support needs to be applied first; then we can work toward more specific stratagems as we learn what is going on in the body and instigating seizure activity. Each person reacts uniquely to toxins, and discovering individual triggers is difficult—sometimes impossible.

One of the biggest problems with treating seizures is tailoring treatment to the disease, as the medications prescribed are extremely varied and complex and can cause numerous undesirable side effects. Many of these medications make you drowsy or may decrease your ability to focus and concentrate, which in turn can interfere with schooling and other normal activities. One of the biggest benefits of CBD is that it has no psychotropic

effects; therefore, its use in young children can be very helpful. This is especially true for children who cannot understand what you are trying to explain to them about medications, side effects, and psychotropic activity. High doses of THC can and likely will trigger psychotropic activity. This can increase fear, anxiety, or even produce paranoia. This is why I usually start with low-dose CBD on younger children. Whenever possible, the discussion of the medications should be carried out with the child who is receiving them. The goal is to help control seizures without creating other problems for the individual.

One of the biggest contributions CBD can make is through the control of cell excitement. When you can make cells less excitable, you can help to reduce seizure activity. Cannabis has applications for both partial and generalized seizures, and, because CBD is nonpsychotropic, it has low toxicity and a high tolerability in humans.⁶ CBD elicits seizure control through multiple mechanisms of modulating neuronal excitability. It exerts a bidirectional regulation of Ca²⁺ plus homeostasis, accomplished through mitochondrial activity that involves Na⁺/Ca²⁺ ion exchanges. This activity can either increase or decrease cytosolic calcium levels and will depend on the neurons' activity—either normal physiologic activity or a highly excitable state.¹

CBD is an agonist or stimulates positive activity at 5-HT_{1A} receptors (HT stands for hydroxytryptamine).²⁻⁶ Activation of these receptors will elicit membrane hyper-polarization, which in turn inhibits seizure generation.^{7,8} These receptors are a subset of serotonin receptors.^{7,8} CBD further acts by increasing the active adenosine levels in the CNS by reducing the adenosine reuptake.^{9,10} The reduction of adenosine reuptake increases the inhibitory adenosinergic tone to help further suppress seizures. CBD also acts as an antagonist at CB₁ receptors, inhibiting the presynaptic terminals that may increase GABA release. This in turn helps to decrease endocannabinoid tone and thereby helps increase the level of inhibition for other seizure activity.¹¹

Other CBD activity includes the blocking of breakdown of anandamide

by FAAH and the reuptake of this compound into the neuron. This activity produces CB1 receptor agonism.¹²⁻¹⁴ CBD can also block low-voltage activated (T-type) Ca²⁺ ion channels, further helping to modulate neuronal excitability.¹⁵ CBD increases and modulates the activity of glycine receptors, which further reduces excitability of the neurons.¹⁶

In experimental studies, CBD is shown to be effective against grand mal seizures, cortical focus seizures, complex partial seizures, and temporal lobe epilepsy.^{6,17} In my practice, I try CBD as a first-line treatment. I have had great success with seizure control with CBD alone. I also have many patients whose seizures have stopped; then slowly, over time, we've been able to reduce and eliminate the seizure medications. What I have seen is that each patient is different, and that we need to work together to eliminate the causes that can be remediated. Looking at the whole individual and addressing any other support needs that they have is imperative.

It is always best to begin with a low dose and then gradually increase. Once you find the sweet spot, the dose will usually be consistent because the body does not build tolerance to CBD. Given the wide variety of seizures, some individuals will require tinctures of both CBD and THC. There are multiple ratios of CBD and THC, and each will have its own efficacy, so we need to work to find the right balance. Fortunately, the CBD helps reduce the psychoactivity of the THC. The higher the amount of THC, the greater the likelihood it will trigger psychoactive reactions, which will limit the efficacy. In many studies, side effects were only seen when THC was used.

I was once asked whether CBD could be used in a particular case of a 17-year-old who had had seizures for 12 years and been on multiple medications. "Frank," as we will refer to him here, had had all the side effects. His history was clean with no big infections, but he did have some anxiety.

My colleagues and I looked at neurotransmitters and they were low. We began to address the neurotransmitter issues and saw a lessening of the anxiety and an improvement in focus and concentration. We then began a

low dose of CBD, and the breakthrough seizures Frank was having stopped.

We continued the low dose and then began to reduce one of his medications, slowly tapering it until Frank was no longer getting that medication. He was doing well, with no seizures, and beginning to feel happier and more involved. We began to taper the second medication, and he did well through the first three drops. With the fourth drop, he had a seizure—very short and different from his previous ones.

We then went back up a step on the medication and held there for a couple of weeks. The third week we raised his CBD and waited for two weeks. We then began to taper the medication again. He did well, having no seizures, and the fatigue he'd had for years began to lift. The fatigue was a side effect of the medication. He is now only on CBD and seizure free. He no longer has anxiety, and his focus and concentration are better than ever before.

In sum, each person will respond individually to cannabis, and the dose he or she will need, as well as the particular combinations of CBD and THC, will differ for each individual who has seizures. In addition, medications must be gradually tapered to enable the body to adjust, and no medication should be stopped abruptly.

VII

Neuroprotection

In treating today's neurological diseases need a variety of approaches. Neurological diseases, such as Parkinson's, Huntington's, Alzheimer's, and multiple sclerosis, have some common threads that need to be addressed. Each of these diseases attacks and destroys neurons, creating inflammation in the brain and thus affecting all other systems. One of the major objectives in treating these diseases has to be to protect neurons from damage and to further reduce neuroinflammation. The endocannabinoid system can address several of the prominent issues across these diseases.

The endocannabinoid system is an avenue that supports intercellular communication.¹³⁷ The endogenous cannabinoids and phytocannabinoids can provide neural protection.^{31,39,114,142} This neural protection is provided through both cannabinoid and noncannabinoid receptors. Their activity with glial cells can provide anti-inflammatory action through the cannabinoid receptors. This activity can help reduce excitotoxicity through the reduction of glutamate release. These compounds also provide mitochondrial stabilization, controlling free cytosol Ca²⁺ ions. This activity will help both reduce oxidative stress and create better blood supply.

CB2 receptor signaling pathways help reduce cyclic adenosine monophosphate (cAMP)¹²⁷ and stimulate prosurvival pathways. This has been demonstrated in rat oligodendrocytes,¹²¹ in rat RBL2H3M1 mast cells,¹³¹ mouse neural progenitors,¹²⁰ and the MAPK cascade. Research has shown that CB2 receptor stimulation in rat microglial cells⁴ led to cell

proliferation and survival of these cells. The same pathway has been demonstrated to help human monocytes¹²⁹ and leukemia cells.¹³⁰ The same prosurvival pathways have been shown to be activated in many other cell types in the body, including pancreatic cells.¹³³

For neuronal protection, CB2 stimulation depends on the cells' differentiation. The reaction to CB2 the reaction to CB2 receptor stimulation will depend on the cells level of differentiation; some cells will go backwards and de-differentiate and move into a proliferative phase, this has been seen in some Glial malignancies and breast cancer.^{89,141} In the cancer cells, this stimulation increases death of cancer cells while at the same time protecting normal neuronal cells from damage.

The cannabinoids help modulate the immune system, which is a large contributor to the neuroinflammation and destruction in the neurodegenerative diseases. The cannabinoids can cross the blood-brain barrier and be directed specifically at the CB2 receptors. When there is inflammation in the brain, the number of CB2 receptors on the microglial cells increases; these cells are the generators of the cascade of inflammation.¹ Microglia are macrophage-like cells in the CNS; these cells may participate in the regeneration or the degeneration of the CNS. In the activated state, the cells have specific cell surface receptors; a multitude of different kinds of receptors contribute to their activities, whether inflammatory or anti-inflammatory. When they are activated, they have an increased number of CB2 receptors.

Depending on the stimulation and activation status, these cells can either increase the inflammatory process or they can help to reduce the proinflammatory cytokine production and activation of other cells.⁴ The proper stimulation of CB2 receptors can help reduce their proinflammatory activities. There are CB2 receptors on many cell types in the CNS.^{11,20,116,120,121} When there is inflammation present, there is an increase in the number of CB2 receptors increases, which can help stop neurodegeneration.⁷⁻¹² Diseases in which this would be applicable

include multiple sclerosis, amyotrophic lateral sclerosis (ALS), hypoxic-ischemic encephalopathy, Alzheimer's disease, neuropathic pain, and HIV encephalitis.

In this chapter we look at several of these diseases and the activity of cannabinoids. When there is neuroinflammation, there is always an increase in the number of CB2 receptors. However, in early inflammation, there can be a temporary increase in CB1 receptors; in this case, the number is reduced.¹⁵⁻¹⁷ It has been shown that the increase in CB2 receptors occurs early in the process of inflammation.^{6, 20-22} This increase in their production has been shown to help reduce the production of proinflammatory cytokines by the microglia.²³⁻²⁹ So from this research it becomes clear that the CB2 receptors are the ones that can help control the whole neuroinflammatory process.

Some of the neural-protective effects from some of the phytocannabinoids are active through other types of receptors.³¹ Some of these compounds can help block the release of glutamate by N-methyl-D-aspartate (NMDA) receptors (NMDARs); by blocking or reducing this release, they decrease the excitement in the neurons and help to reduce neuroinflammation. They can also stimulate the production or release of GABA; this activity may help improve blood supply to the injured brain.³²⁻³⁴ These cannabinoid compounds also control and help improve glucose utilization, protecting the cells' energy processes.^{35, 36} By reducing the amount of glutamate released, these compounds reduce excitotoxicity, thereby helping to save and protect neurons.³²⁻⁴⁴ Part of this activity is controlled by CB1 receptors; they act presynaptically to help reduce glutamine release.⁴³ If the CB1 receptors are blocked, release of glutamate and toxicity can increase;^{32, 38, 44} therefore, compounds that stimulate CB1 receptors can increase the neurotoxicity.⁴⁵⁻⁴⁸

The cannabinoids help modulate calcium influx, which helps to control glutamate receptors and reduce excitotoxicity.³⁷ This neural protection is further aided by the antioxidant power of some of the cannabinoids, which

reduce oxidative stress.^{59, 60} The natural antioxidants that we have—including vitamin A, vitamin C, vitamin E, and ubiquinol—are not present in adequate amounts to handle the increase in free radicals. These ROS are independent of the cannabinoid receptors.^{32-34, 60-63} From just its chemistry, CBD is a more potent antioxidant than vitamin C and vitamin E.⁶³ Therefore, by increasing the endocannabinoid levels and by blocking the reuptake and degradation, CBD provides excellent antioxidative protection.⁶⁴⁻⁶⁷

In all the studies, the phytocannabinoids have been able to reduce inflammation and provide antioxidant protection.⁶⁸ In the process of reducing microglia activation, they also reduce the activation and proinflammatory status of astrocytes.⁶⁹⁻⁷⁶ Astrocytes are deactivated from proinflammatory stimulation and then become quiescent or anti-inflammatory.⁷⁰ This has been shown to be supportive in demyelinating diseases, such as multiple sclerosis.³²⁻⁷⁷ In all of the neuroinflammatory diseases studied, the cannabinoids have been able to reduce inflammation.^{32-34, 49, 69, 78} It has been shown that stimulation of CB2 receptors help reduce neural inflammation and the inflammatory lesions that are produced.⁸⁷⁻⁹³ The lesions are produced from the inflammation destroying neurons.

Many of the cannabinoids have shown the potential to convert an inflammatory process, reducing inflammatory cytokines, and reducing microglial activation, which helps support the survival of astrocytes, oligodendrocytes, and stem cells. This sets the stage for possible repair and regeneration. All of these have been shown to be part of the activity that CBD can accomplish. On each front where neural degeneration occurs, cannabinoids have been shown to reduce damage, protect normal cells, and even protect stem cells and increase regenerative processes. In the following chapters, we look at each of these diseases and explore how these compounds can help reduce the damage that is caused by the disease process itself.

VIII

Alzheimer's Disease

Alzheimer's disease is an age-related neurodegenerative disorder associated with cognitive decline. The disease affects 10 percent of the population over 65 years old and 25 percent of the population over 80 years old.⁷ A small proportion of Alzheimer's disease has a genetic basis, while most occurrences are sporadic.⁵ The disease is associated with neural inflammation, excitotoxicity and oxidative stress and has several hallmarks.^{5, 6, 8}

The first of these hallmarks is the deposition of beta-amyloid proteins called senile plaques. Early in the disease, senile plaques are formed in the hippocampus, cerebral cortex, and amygdala, leading to memory loss and behavioral changes.¹⁰ These plaques are located outside the cells and consist of 1 to 42 amino acid peptides. The abnormal processing of these transmembrane amyloid precursor proteins has the central role in the genesis of Alzheimer's⁹ and can evoke neuronal cell death along with the involvement and disruption of cleavage-enzyme activity.¹⁰⁸ Beta-amyloid production acts as a seed for new beta amyloid production.¹⁰⁹

The immune cells, or microglia, of the brain start to activate and surround the senile plaques, working to clear the beta-amyloid plaque by phagocytosis.¹³ They are not capable of completely removing the plaques, though, which leads to their prolonged activation and production of proinflammatory cytokines, such as IL-beta.^{14, 15} Local inflammation causes an increase in the processing of amyloid precursor protein, which in

the end generates more beta-amyloid.¹⁵

Activated microglia have direct toxic effects.¹⁶ At the edge of the senile plaque, the cells involved generate ROS that cause oxidative damage to the brain.¹³ Damage to cholinergic neurons will affect the brain's activity, and some use of acetylcholinesterase inhibitors will block the breakdown of acetylcholine. These compounds only help with mild cognitive impairment.

The second hallmark for the disease is the hyper-phosphorylation of tau protein producing nitrate tau protein,^{6, 106, 107} which may become microtubule-associated proteins.¹¹

Chronic inflammation is the third hallmark for Alzheimer's disease. This process leads to activation of both microglial cells and astrocytes. When these cells are activated, they produce and release proinflammatory molecules.^{82,83} These molecules perpetuate the reactive gliosis, which can lead to increasing damage and, ultimately, cell death of neighboring neurons. This process leads to expanding and self-perpetuating neuroinflammation.⁸⁴ This cycle promotes neuronal death requiring intervention to reduce reactive gliosis and decrease or prevent activation of microglia and astrocytes.

These combined processes evoke activation of the microglial cells, some neuronal cell death, and impaired interneuronal communication. From these two processes, inflammation begins. Nonsteroidal anti-inflammatories in the long term can reduce some risk.¹² They have been shown to slow the onset of disease and may help to reduce the severity. With inflammation, an increase in oxidative stress leads to oxidative damage¹¹⁶ that can affect lipids, proteins, and nucleic acids. This is also accompanied by a dysregulation of intracellular calcium,¹⁷ excitoxins, and cholinergic neuron damage. These activities also produce mitochondrial defects that lead to the increased production of ROS and reactive nitrogen species (RNS).¹¹⁰⁻¹¹²

These combined producers of inflammation also lead to an imbalance in transitional metals, including copper, iron, and zinc.¹¹⁶

In Alzheimer's disease, there is an up-regulation of microglia in the areas of senile plaques. These cells are producing proinflammatory cytokines and recruiting and activating more immune cells. The microglial cells also have an increased number of CB2 receptors.^{26, 28} Activation of cannabinoid receptors and noncannabinoid receptors in the activated glial cells reduces the production of proinflammatory cytokines, which helps reduce the whole inflammatory process.⁶² This may be through control or other effects on transcription factors, such as nuclear factor kappa B (NFκB)^{56, 63} Cannabinoid receptor stimulation causes a down-regulation of transcription factors involved in the induction of and promotion of inflammation in neurodegenerative diseases. Activation of cannabinoid receptors leads to stimulation in the production of anti-inflammatory cytokines, such as interleukin-1 receptor antagonist (IL-1ra).⁶⁴

Rats with beta-amyloid injections develop inflammation and cognitive impairment. These could be reversed early by using CB1 or CB2 receptor agonists.²⁶ CB2 receptor stimulation helps to deactivate the activated microglia²⁶ and increases the removal of beta-amyloid by macrophages.¹¹⁴ CB2 receptor stimulation can also suppress the immune system.⁶⁵

The endocannabinoid system, with AEA and 2-AG, is in the brain. It contains the enzymes for production, proteins for transport, enzymes for degradation, and CB1 and CB2 receptors. These compounds do not act only on cannabinoid receptors. Dronabiol is an oil-based solution of delta-9-THC,¹⁸ a compound that has been used and shown to decrease disturbed behavior, stimulate appetite, and alleviate nocturnal agitation in some patients.¹⁹

The cannabinoid system provides antioxidant and anti-inflammatory activity and neuronal protection.²⁰ CB1 receptors are abundant in the brain, found heavily in the hippocampus, cerebral cortex, and cerebellar basal ganglia.²¹ Those found in the hippocampus affect learning and memory²² and participate in cognitive processes. If they are disrupted

early, they will affect neural plasticity. No change has been noted in the number of these receptors near the senile plaque in patients with Alzheimer's.^{27, 28}

CB2 receptors are found on neurons in the brain stem²³ and cerebellum²⁴ and on microglia.²⁵ In patients with Alzheimer's, an increase in CB2 receptors on the microglia has been noted, as well as in the microglia surrounding a senile plaque.²⁶ The cannabinoid receptors in the process of Alzheimer's disease become nitrosylated, which impairs their downstream coupling and, therefore, their activity.²⁶

FAAH is found to be up-regulated in senile plaques.²⁸ This enzyme metabolizes anandamide (AEA), which leads to an increase in anandamide metabolites, such as arachidonic acid. This may also lead to an increase in prostaglandins and other proinflammatory molecules. FAAH in astrocytes leads to the process known as reactive gliosis in the area of beta-amyloid plaques.²⁹ Neuronal damage increases the production of endocannabinoids.^{30, 31} The cannabinoid tone helps influence neuronal survival. Boosting the cannabinoid system can help offer protection against beta-amyloid production and storage.

Beta-amyloid³² induces hippocampal degeneration and causes gliosis, resulting in cognitive decline. Increased production of 2-AG is the result of cells trying to protect themselves. This increase in production decreases neurotoxicity and prevents memory impairment. Early administration of reuptake inhibitors of anandamide and noland ether, another endocannabinoid, helps reduce beta-amyloid neurotoxicity through the activation of CB1 receptors and the extracellular regulation of kinase pathways.³³

Memory is affected by events in the hippocampus. Cannabinoids that are CB1 receptor stimulants actually decrease the performance of memory in rodents.³⁴ This effect is possibly from the reduction in acetylcholine.³⁵ CB1 receptor antagonists have been shown to improve memory performance.³⁶ CBD is an antagonist (blocker) of CB1 receptors. Some of

the memory impairment that is evoked by beta-amyloid is reversed by cannabinoid antagonism at CB1 receptors.³⁷ However, the CB1 blockade has been shown to increase the neurodegenerative components.

In Alzheimer's disease there is dysregulation of intracellular Ca²⁺; this can create excitotoxins within the neurons. There is also excessive activation of NMDARs. These are a subtype of glutamate receptors that when activated, create more excitotoxicity.^{38, 39} In the inherited form of Alzheimer's, there is a mutation in the presenilin genes (PS1/PS2) that causes a disruption in calcium signaling.³⁸ This contributes to neurodegeneration in memory impairment.⁴⁰ Beta-amyloid can itself directly increase voltage-dependent Ca²⁺ channel activity.⁴¹ It can also create Ca²⁺-permeable pores in the cells.⁴² This further increases the intracellular Ca²⁺ imbalance and is part of the pathologic mechanism.

Beta-amyloid reduces glutamate uptake by astrocytes, which further increases the activation of glutamate receptors and leads to excitotoxicity.³⁹ Part of the narrow protection that is provided by CBD is from the reduction and control of Ca²⁺ influx. This process helps reduce or limit the excitotoxicity. Cannabinoids provide some modulation of NMDA receptors⁴³ and the modulation or inhibition of presynaptic Ca²⁺ entry.^{44, 45} They also suppress excess glutamatergic activity.^{46, 47} CB1 receptor activation can inhibit glutamate release and thereby reduce excitotoxicity.⁴⁸

The endocannabinoid production of AEA and 2-AG depend on Ca²⁺ movement in the postsynaptic cell.^{39, 40} The endocannabinoids are produced and provide more feedback control of neurons to reduce excitotoxicity.⁵⁰ Inhibition of Ca²⁺ intracellularly is partially controlled by reducing calcium release from ryanodine-sensitive stores.⁵¹ Controlling Ca²⁺ levels through cannabinoid receptors provides access to a pathway that stimulates production of protein kinase A, reduces production of nitric oxide,⁵² and increases brain-derived neurotrophic factor (BDNF).

BDNF will increase neurogenesis and help protect neurons against excitotoxicity.⁵³

Nonneuronal cells help create the induction of nerve growth factor (NGF). This is induced by cannabinoids acting at CB1 receptors. This stimulation activates several pathways that contribute to neuron protection and CB1 receptor stimulation by 2-AG or anandamide coupling to assist in the production of axonal growth response.¹³

CBD is an antioxidant. It helps to provide neuroprotection against glutamate toxicity.⁵⁵ It helps to reduce the induction of inducible nitric oxide synthase (iNOS).⁵⁶ It further helps prevent the activation of stress-activated protein kinase p38.⁵⁶ It also helps prevent the inflammatory transcription factor, NF κ B.⁵⁶

CBD also helps to down-regulate inflammatory signaling with beta-amyloid plaques.⁵⁷ This helps reduce beta-amyloid-induced neuronal damage by scavenging ROS and reducing lipid peroxidation. The antioxidant properties are independent of CB1 receptors. CBD can reduce and reverse tau hyperphosphorylation.⁵⁸ This is accomplished by reducing phosphorylation of glycogen synthase kinase-3 beta. This is a tau kinase responsible for tau hyperphosphorylation. This works through the Wnt/beta-catenin pathway. Reducing glycogen synthase kinase-3 beta causes a reduction in the amount of precursor protein being converted to form beta-amyloid.⁵⁹ This leads to a reduction in the amyloid burden.

CBD can help prevent beta-amyloid effects by reducing tau hyperphosphorylation and oxidative stress, which in turn lead to reducing neuroinflammation and preventing neuronal apoptosis. This compound is devoid of any psychoactivity, and its activities are carried out even when the CB receptors are nitrosylated in the Alzheimer's brain. Since the cannabinoid receptors are not used by CBD, there is no issue with the uncoupling and other downstream activity.²⁶ The modulation of microglial activity and cell functions do not depend on CB receptors.¹¹⁵

CB2 receptors have a large population in microglia,²⁵ as well as in the

neuronal populations in the brain stem and the cerebellum.²⁴ These receptors influence neuron and other cell survival.⁶⁰ Neural protection is assisted through their anti-inflammatory actions.⁶¹ These receptors are up-regulated in activated microglial cells and astrocytes. They help control the local proinflammatory mediator, interleukin-1 beta, as well as ROS and prostaglandins.

Delta-9-THC competitively inhibits acetylcholinesterase.^{73, 74} This works to increase the amount of acetylcholine and helps reduce beta-amyloid peptide conversion into fibrillar species. It also helps reduce beta-amyloid plaque production. Therefore, cannabinoids can reduce oxidative stress, reduce neural inflammation, and prevent neuronal death. These complications are produced by beta-amyloid. The cannabinoids stimulate the intrinsic healing mechanisms of the brain.

The endocannabinoid system helps regulate neurogenesis.⁷⁰⁻⁷² Adult neurogenesis is seen in the dentate gyrus of the hippocampus and the subventricular zone.⁶⁶ In mouse models of Alzheimer's disease, neurogenesis is reduced,⁶⁷ while in postmortem Alzheimer's disease patients there is hippocampal neurogenesis.⁶⁸ In animal models, the only things that helped to enhance neurogenesis were dietary restriction and increased BDNF.⁶⁹ Both of these led to improved memory.

In addition to helping with neurogenesis regulation, the endocannabinoid system also helps to reduce anxiety and has antidepressant-like effects. These compounds stimulate neuroprogenitor proliferation.⁷¹ They also help with adaptation to neuronal stress by reducing or limiting excitotoxicity. Their potential is in providing long-term progress through neurogenesis.⁵

CBD works in Alzheimer's even though the cannabinoid receptors are modified and not usable. CBD functions through nuclear receptors^{77, 78} to reduce inflammation, oxidative stress, lipid peroxidation,⁵⁷ and neuronal cell death. These nuclear receptors are present in the CNS, and

they are increased in Alzheimer's disease.^{80,81} CBD further provides stabilization of calcium levels and provides protection for mitochondria. This protection comes through membrane stabilization of the mitochondria, reduction of endoplasmic reticulum stress, and maintenance of cytochrome enzymes so that energy production is continuous and efficient. CBD further helps produce anti-inflammatory effects through adenosine A2A receptors and serotonin 5-HT1A receptors. Through these activities brain function improves.⁸⁵⁻⁸⁷

In conclusion, cannabinoids offer some significant help for the Alzheimer's patient. With the present research, there is also an early window for THC to be effective. CBD has been shown to provide support for extended periods of time. It will be interesting to see what new research will provide into the possibilities of the "entourage" effect with other cannabinoids. This research is in its infancy, and the possibilities are endless.

IX

Parkinson's Disease

Parkinson's disease is a form of neural degeneration. The neuropathology exhibits bradykinesia, rigidity, postural instability, and tremor. The tremor and some of the instability are due to the progressive degeneration of dopaminergic neurons in the substantial nigra pars compacta. When these neurons are affected, this leads to a dopaminergic denervation of the stratum.^{1,3} Oxidative stress, mitochondrial dysfunction, inflammation, and creation of a metabolic syndrome contribute to the underlying process.⁴⁻⁶ There is also a further dysfunction of the ubiquitin-Proteasome system⁸⁴ and the formation of intracytoplasmic inclusion bodies referred to as Lewy bodies. These are round eosinophilic intracytoplasmic proteinaceous inclusions.⁸⁴

The use of the medication L-dopa as replacement therapy for dopamine loss is the most common treatment used today for mild cases, but over time it induces an irreversible dyskinetic state with involuntary movement.⁷ The search at present is for pharmacological interventions that can delay or arrest the progressions of Parkinson's disease.^{8,9} The specific goal of these interventions would be to reduce excitotoxicity, modulate calcium influx, reduce oxidative stress, and reduce neuroinflammation.

Cannabinoids provide a method of giving long-term help with protection, and they can also initially enhance motor symptoms.¹⁰⁻¹² Some evidence exists of overactivity of the endocannabinoid transmission

in the basal ganglia at some point in Parkinson's disease.¹³⁻¹⁵ CBD has been shown to cause an up-regulation of copper-zinc superoxide dismutase. This produces a reduction in oxidative stress and does not depend on the cannabinoid receptor. CBD can provide further neural protection against the progressive degeneration of the nigrostriatal dopaminergic neurons in Parkinson's disease.¹⁶ The mechanisms by which this is accomplished are a combination of several different receptors: cannabinoid, TRPV1, and adenosine A2A.

Neuroprotection in the human basal ganglia has been correlated with the ratio of N-acetylacetate to total creatinine. CBD in the putamen and globus pallidus in recreational cannabis users was shown to enhance neuronal and axonal integrity.¹⁸ CBD has been used as an effective antipsychotic in Parkinson's disease at a dose of 150 milligrams (mg) per day and decreased the progression of Parkinson's as well.¹⁹

CBD provides antioxidant activity from its own chemistry. It provides no protection through peroxisome proliferator-activated receptors (PPARs); these are nuclear receptors that control gene transcription. CBD inhibits caspase 3 generation from its inactive precursor procaspase 3, providing protection from activation of the cell death cycle that leads to apoptosis. In this process, CBD is providing protection for neurons.²⁰ CBD also decreases adenosine uptake by macrophages and microglial cells by blocking the equilibrative nucleoside transporter 1. This then causes the activation of adenosine A2A receptors, creating an immunosuppressive action on the microglia and the macrophages and a decrease in TNF-alpha.⁸⁰⁻⁸³ The decrease in TNF-alpha reduces both oxidative and nitrosative stress, as well as the mitochondrial superoxide generation induced by high glucose. There is a further reduction in production of the NF-kB protein in the endothelial cells, reduced nitro tyrosine formation, and prevention of the expression of iNOS. CBD also prevents the expression of the adhesion molecules ICAM-1 (an intercellular adhesion molecule) and VCAM-1 (a vascular cell adhesion molecule) by the endothelial cells; by preventing the expression of these compounds, CBD

helps limit new inflammatory-promoting cells from entering into the tissues.⁸³

CBD also attenuates dopamine depletion, accomplished by a reduction of tyrosine hydroxylase deficits⁸⁵ and indicative of a degree of narrow degeneration. With a newer perspective, we can measure the correlation between N-acetyl aspartate and total creatinine. When this ratio is elevated, there is increased neurogenesis and synaptogenesis,⁸⁵ and a decrease in copper-zinc superoxide dismutase. This enzyme is an endogenous defense against oxidative stress. CBD has also been shown to reduce striatal atrophy.

Several factors indicate an increased risk for the development of Parkinson's disease. There is some genetic susceptibility, seen through alpha-synuclein that has a tendency to fold; when it folds it is less likely to be broken down and removed. Usually, conformational plasticity is greater, and these proteins can stay single, fold, or form into monomeric or oligomeric compounds. With the more complex folding, they become more stimulating for the production of problematic compounds. The complex compounds are more likely to form into amyloidogenic filaments that cause more cell damage.⁸⁶

These filaments are highly expressed in mammalian brains, and are increased in presynaptic nerve terminals and associated with cell membranes and the secular structures.⁸⁷ They are also associated with membrane microdomains-lipid rafts; these are used for synaptic localization⁸⁸ and assist in synaptic vesicle recycling and dopamine neurotransmission.⁸⁹ In synaptic vesicle recycling, it is shown that alpha-synuclein support the function in recycling and dopamine neurotransmission.⁹⁰ CBD also binds to and blocks the activity of phospholipase D (PLD).⁹¹ This helps regulate lipid metabolism by protecting lipid droplets from hydrolysis.⁹² CBD helps to regulate the size of presynaptic vesicle pools⁹³ and alpha-synuclein. The CBD also helps to regulate the size of synaptic vesicles, which store and recycle

neurotransmitters. They also assist in recycling, particularly neurotransmitter dopamine, for storage, release, and recycling.

The alpha-synuclein oligomers are precursors for higher-order aggregates, which are amyloid-like fibrils referred to in Parkinson's disease as filamentous structures in Lewy bodies and Lewy neuritis.⁹⁴ The monomers can form annular fibrils or combine into protofibrils to form Lewy bodies.^{84,95} Similar to pore-forming bacterial toxins, annular fibrils can open pores into the cells.⁹⁶ These protofibrils may cause more cell membrane permeability; and the catecholamines, especially dopamine, can react with alpha-synuclein to form covalent bonds. There can be a slow conversion of protofibrils to fibrils,⁹⁷ and protofibrils may be cytotoxic.⁹⁸ The cytotoxicity seen with fibrils and inclusion bodies⁹⁹⁻¹⁰¹ promotes the formation of more alpha-synuclein.¹⁰¹⁻¹⁹⁵

The increased production of alpha-synuclein starts to affect mitochondrial complex 1, acting as an inhibitor—along with rotenone and paraquat—and creating more oxidative and nitrosative stress.¹⁰⁶ This leads to more oxidative damage and selective tyrosine nitration of the alpha-synuclein in Parkinson's disease.¹⁰⁷ The tyrosine nitration of alpha-synuclein promotes further fibril formation of unmodified alpha-synuclein. This leads to a decreased rate of degradation of the 20S proteasome and cysteine protease calpain 1.¹⁰⁸

An increase of alpha-synuclein in the human substantia nigra happens with age, and this process needs stabilization to prevent accumulation and to reduce oxidative stress. Without intervention, the oxidative stress can lead to protein modifications.

The major damage in Parkinson's disease is from oxidative stress, hyperexcitability, and reduced energy production from mitochondrial damage. These have been shown to be addressed by cannabinoids, especially CBD. The protection is from CBD's direct effect on neurons and its effect on the glial cells. It is through the use of cannabinoids that we may see advances made in the treatment of Parkinson's disease. It has been shown that the cannabinoids can prevent damage to the dopaminergic

neurons, or even their death.

X

Huntington's Disease

Huntington's disease is an inherited neurodegenerative disorder. The normal gene for huntingtin protein is present but when you have the disease you have additional material in the form of repeats of CAG; the more of the repeats you have, the more severe the problem. Called the huntingtin gene (HTT), in the genetic coding C=cytosine, A=adenine, and G=guanine. There is an elongated stretch of glutamine near the NH₂ terminus of the protein,² and the 6 through 35 repetitions of this segment are very unstable with a tendency to expand from one generation to the next.^{19,20} The absolute numbers of this expansion affect the severity and progression of Huntington's disease. Those with 40 or more CAG repeats will exhibit Huntington's disease.² When there are 60 or more, the disease develops in childhood or during the juvenile period.^{2, 21, 22}

A mutation in the huntingtin protein is the triggering event for the development of Huntington's disease. These mutated proteins cause toxic functions and will affect some specific subpopulations of neurons in the stratum, leading to chorea. In the cerebral cortex, they create cognitive deficiencies and lead to dementia. These mutated proteins create brain neurodegeneration leading to a loss of efferent medium spiny neurons. In the stratum, GABAergic neurons are affected by the mutated proteins located in the caudate nucleus, putamen, and medium-sized spiny neurons. Atrophy and loss of cells is prominent in the caudate and putamen.^{3,9}

In 1985, Dr. J. P. Vonsattel created a grading system based on neuronal

location and severity of neuronal loss. Four classes are based on the basal ganglia,³ with classes three and four seeing the broadest effects. In the cerebral cortex, layers three, five, and six are affected, with additional ones noted in the globus pallidus, thalamus, subthalamic nuclei, substantia nigra, white matter, cerebellum,⁹ and hypothalamus.^{10, 11}

Widespread neurodegeneration also involves cortical structures.⁴⁻⁶ The mutation leads to an impairment of the ability of normal huntingtin protein to perform its normal and fundamental activities. These activities support the survival and functioning of the neurons that degenerate within the CNS.^{7,8} These can produce cognitive deficits in attention, working memory, and executive function.¹²⁻¹⁵ Large reductions in the brain's volume occur^{4, 16} before any symptoms are noted from the abnormalities in the cortex. Adult onset usually occurs between 35 and 50 years of age. In cases of juvenile onset, it will occur before 20 years of age with an approximate 10 percent paternal transmission.^{17, 18} Symptoms include personality changes, generalized motor dysfunctions, and cognitive decline.

The normal function of huntingtin protein contributes to polyQ forms that bind to transcription factors.²⁵ Through these factors, this protein supports cell longevity and energy status and associates with mitochondria, golgi, and the endoplasmic reticulum.^{26,27} It can also associate in the nucleus,²⁹ where it helps to modulate calcium homeostasis.²⁷ The mutant huntingtin protein aggregates in neurons, both intracellular and intranuclear. This can affect the cells' autonomous actions²³ and cell-to-cell interactions.²⁴ The process can lead to activation of NMDA receptors, creating excess excitation.

Huntington protein is highly expressed in cortical pyramidal neurons of layers 3 and 5. These neurons project to striatal neurons.²⁸ It associates with vesicular structures within the indissoluble compartments and microtubules.³⁰ Its function here is to promote the production of BDNF

and to transport it along microtubules.³² The protein also helps support the cytoskeleton and participates in morphogenesis, supports endocytosis and exocytosis, and participates in modulating cell apoptosis. It helps to regulate synaptic activity, as multiple repeats in the protein can impair synaptic transmission. It participates in the modulation of gene transcription^{25, 31} and helps to regulate cerebral spinal fluid.³³ It is also critical in participating in the modulation of mitochondrial function.

With the loss of wild-type (normal) huntingtin protein, the neurons' ability to survive is reduced, as is the ability to remove the toxic effects created by the mutant protein.³⁶ Wild-type huntingtin protein reduces the toxicity of the mutant huntingtin protein.³⁷ There is a reduction in the production of BDNF gene transcription,³⁸ which leads to a loss of BDNF that is provided to the striatal neurons (medial spinal neurons, or MSNs).

The BDNF protein is produced in the cortex and moved in an anterograde transport along the cortical striatal tract to the MSNs.³⁹ The BDNF is needed for nerve cell growth and survival, and the mutant huntingtin protein reduces its production.⁴⁰ The repressor element-1 transcription factor/neuron restrictive silencer factor (REST/NRSE) begins to accumulate in the nucleus, which reduces the transcription of BDNF.⁸ There is also a reduction in BDNF vesicle transport³² that leads to reduction in the MSN soma size, and the development of fewer dendritic spines and thinner dendrites.⁴¹

During this process, excitotoxicity and a dysfunction in neuronal interactions and circuits are increased, also noted in the cortical striatal synapses. Excess glutamate receptor activation leads to increased glutamate release from the cortical afferents that is further aggravated by reduced glial cell uptake. We see a loss of NMDARs,⁴² and increased sensitivity in the remaining ones.⁴⁵

The presence of mutant huntingtin protein increases the sensitivity of the neurons to excitement¹ and leads to impaired synaptic plasticity,⁴³ which is necessary for modulation and adaptation to change. There is also

a loss of connectivity between the cortex and stratum,⁴⁴ and dysregulation of calcium storage in the mitochondria, creating mitochondrial swelling. This is accentuated by mutant huntingtin protein, which affects transition pores⁴⁷ and leads to a release of cytochrome c and apoptotic-inducing factor (AIF).⁴⁶

The neurotransmitter system contributes to the cortical striatal connections. Neuron activity can affect glutamate release, and in Huntington's disease both adenosine A2A receptors and input to these receptors is noted with an increase in receptor density in the striatum. There is also increased adenylyl cyclase activity, further increasing excitotoxicity.^{49,50} Cannabinoid receptors⁵¹ and, in particular, CB1 receptors, can increase glutamate release. This can add to an increase in excitotoxicity. Dopamine can directly control glutamate release through D2 receptors, and these may stimulate glutamate release.⁴⁸ There is a parallel between dopamine and glutamine activity. It has been shown that dopamine receptor antagonists improve the symptoms of Huntington's disease.¹

Huntingtin protein is cleaved by caspases 1, 2, 3, and 7. Preventing these cleavages from occurring helps decrease the symptoms of Huntington's disease and prolongs the time before neuronal inclusions begin.⁵² Caspase 6 cleavage is very toxic.⁵³ This is a crucial event in the disease process,^{1, 53} and the first step leading to multiple caspase activations.^{1, 53} This leads to the formation of aggregates of the polyQ expansions.⁵⁴⁻⁵⁷

Aggregates are correlated with cell death,^{58, 59} and there is greater toxicity when these are localized in the nucleus.⁶⁰ This leads to the sequestration of transcriptional regulators.^{61, 62} The ubiquitin-proteasome system (UPS) cannot break down the mutant huntingtin protein.⁶³⁻⁶⁵ Aggregates may be formed to protect against the toxic fragment.^{66, 67} The aggregates stimulate the autophagy and help process and clear the mutant protein.⁶⁸ The aggregates are placed in

autophagosomes or autophagic vacuoles. These then merged with lysosomes, resulting in a degradation of the contents. This process protects cells from death.⁶⁹

Mutant huntingtin protein can bind directly to the mitochondria themselves,⁴⁷ contributing to dysfunction and leading directly to altered metabolic activity and altered calcium-induced permeability.⁷¹ The consequent release of cytochrome⁴⁷ leads to reduced efficiency and energy production in the mitochondria. Altered motility⁷⁰ is seen with reduced mitochondrial membrane potential.⁷¹ The mitochondria themselves also become the product of and a target for ROS.⁷²

Dysfunction of lipid metabolism and cholesterol is precipitated by a reduction in transcription of cholesterol biosynthetic pathways.⁷³ This process affects cell membranes, making them more susceptible to ROS. This is complicated by malfunction in membrane trafficking and a dysregulation of myelin formation. All of these have a tremendous impact on synaptogenesis.^{1, 74} The mutant huntingtin protein binds directly to DNA and prevents the transcription of some genes.⁷⁵ There is a hypoacetylation of H3 histones, down-regulating some genes.⁷⁶

Included in the major changes seen in Huntington's disease is a conformational change in the protein from all the poly-glutamine additions. This affects protein-to-protein interactions, the formation of fragments, the formation of aggregates, and the resistance of the mutant protein to breakdown. These combine to lead to transcriptional dysregulation and a reduction in neuronal survival because of reduced BDNF. There is also mitochondrial dysfunction relating to complex II deficiency and calcium imbalance and an interruption in mitochondrial membrane integrity. These issues are further complicated by increasing excitotoxicity, oxidative stress, and glial activation. The glial activation includes astrocytosis, increasing numbers of reactive microglial and local inflammation, which spreads.

CBD can help reduce the hyperkinetic symptoms of Alzheimer's⁷⁷ and

can also protect striatal neurons from death. It offers protection and provides neuroregenerative properties.^{78, 79}

A correlation with the down-regulation in the neurons is a loss of CB1 receptors in the stratum, this leads to a selective destruction of medium-spiny GABAergic neurons.^{80, 81} CBD helps control the release of glutamate,⁸⁸ which occurs in the early phases of Huntington's disease. Inhibition of FAAH increases the stimulation of CB1 receptors.⁹¹ During the inflammation and neurodegeneration, there is an up-regulation of CB2 receptors in glial cells in response to the damage.

The activated astrocytes influenced by CBD have enhanced trophic support.^{79,82} Microglia activated^{78,79,83} through stimulation of the CB2 receptors reduces the astrocytes' cytotoxicity and thereby reduce their production of free radicals and proinflammatory activities.^{79,82} CBD enhances cell survival,^{84,85} provides neuroprotection,^{92,93} and helps to normalize glutamate homeostasis.^{95,96} CBD helps to reduce oxidative stress^{97,98} and reduces or attenuates glial activation. It also helps to reduce local inflammatory events^{99, 100} and helps modulate the effect on genes.¹⁰¹ This genetic intervention helps reduce the stress response and inflammation.

CBD also provides protection and support for the mitochondria. It helps to reduce oxidative stress with its two hydroxyl groups⁹⁴ and also helps to restore normal balance, reducing oxidative stress.¹⁰² Through these activities, CBD works to enhance neuronal survival and normal intracellular mechanisms that support the endogenous antioxidant enzymes and to control the oxidative stress that is generated.⁹¹ This is controlled through CBD's activity with transcription factors, and nuclear factor-erythroid 2-related factor (nrf-2). Through this mechanism, CBD's activity leads to an increase in transcription factors that can respond to oxidative stress.¹⁰²

CBD also provides calcium (Ca²⁺) modulation within the

mitochondria,⁸⁷ accomplished through control of TRPA1 calcium channels, and TRPV1 and TRPV2 receptors.⁹¹ These functions are independent of cannabinoid receptors and some of it is independent of TRPV1 receptors.⁸⁷ Some of these activities are also independent of the adenosine A2A receptors⁸⁷ that help scavenge free radicals.⁸²

CBD also helps induce the reduction in proinflammatory cytokines such as IL-2 and TNF-alpha.⁸⁹ It increases the production of BDNF, which is necessary for neuronal survival.⁹⁰ Some of the anti-inflammatory activities are independent of CB2 receptors, including control of microglial cell migration,¹⁰³ the control of proinflammatory cytokines,¹⁰⁴ and the inhibitory control of NFkB signaling.

CBD controls the genes regulated by inducible nitric oxide synthase (iNOS).^{104,105} It also helps to reduce the phosphorylation of kinases, controls transcription factors, and prevents translocation of the molecules into the nucleus, thereby preventing expression of pro-inflammatory genes.¹⁰⁵ CBD further binds the nuclear receptor PPAR-gamma,¹⁰⁷ which acts to antagonize the action of NFkB. This activity reduces proinflammatory enzymes, such as iNOS, ox-2, cytokines, and metalloproteinases.¹⁰⁷

From this information, it is easy to deduce that CBD can have a pivotal role in the treatment of Huntington's disease. The issues are going to be the recognition of early signs of the disease and when the administration of CBD would be most beneficial. The action of this phytocannabinoid can help address all the issues that are created during the process and evolution of Huntington's disease. From a theoretical point, nothing but benefit that can be derived from the use of CBD in the treatment of Huntington's disease. It is my hope that the studies will be done and that, if this theory is correct, many people will benefit from this intervention.

XI

Multiple Sclerosis

Multiple sclerosis is a chronic inflammatory disorder of the CNS, including the brain, spinal cord, and optic nerves.² Sclerosis refers to scarring,¹ the result of the destruction of the myelin sheath that is the wrapping around the nerves. There are some factors that have been considered to predispose some people to the development of multiple sclerosis,²³ including some genetic predispositions, some viral infections, and a predisposition or development of autoimmunity. In multiple sclerosis, considered an autoimmune disease, myelin is destroyed.⁴ The underlying nerve tissue itself can be damaged or destroyed when the immune system attacks its own body's tissue.¹ One of the biggest issues in this disease is the movement of leukocytes across the blood-brain barrier; when they cross the barrier, they become activated and begin to produce proinflammatory cytokines and cause the escalation of the inflammation in the brain.²⁴

Multiple sclerosis takes several forms,² and the most commonly used classification for the forms is empirical (derived from experimentation). The first and most common form is relapsing-remitting multiple sclerosis (RRMS).² Symptoms can appear for days to weeks and then resolve spontaneously. The bouts reoccur approximately every one to two years. Inflammatory lesions develop and continue to do so even during symptom-free periods. The second form is secondary progressive multiple sclerosis (SPMS). In this form, two preexisting neurological deficits worsen

over time and relapses occur in the end stages. The third form is primarily progressive multiple sclerosis (PPMS)³ This form is characterized by a gradual neurological progression from the onset, with fewer abnormalities appearing on brain magnetic resonance imaging (MRI). It is also less responsive to standard therapies. The fourth form is progressive relapsing multiple sclerosis (PRMS). In this form neurologic function worsens gradually, with subsequent superimposed relapses. This may be a variant of SPMS, with the suggestion that the initial relapses were unrecognized or clinically silent. Some speculate that relapses are forgotten by the person.

Multiple sclerosis usually begins between the ages of 20 and 40 years.¹ It is usually seen with recurrent bouts of central nervous inflammation² and damage to the myelin sheath around axons (known as demyelination). The damage may even affect the axons themselves.⁵ In demyelinating lesions, there are more than 11,000 transected axons per cubic millimeter; the normal brain has fewer than 1/ per cubic millimeter.² Transected neurons can no longer transmit information; this damage is created from the immune system activation and is part of the damage in multiple sclerosis.

Severe demyelination can occur, and the number of axons and oligodendrocytes can decrease. The immune system responds against unknown CNS antigens.² The inflammation that occurs can be generated from T-cell mediated or T-cell-plus mediated autoimmune responses. These are two specific types of T-cells that are found associated with autoimmune disease. One of the primary disorders affects the oligodendrocytes, which produce the myelin.⁴

Cortical demyelination plays a critical role in multiple sclerosis pathogenesis and cognitive dysfunction. These may occur early in the disease.⁶ Oligodendrocytes progenitor cells capable of remyelination have been observed in the white-matter plaques.⁷

The diagnosis of multiple sclerosis has no specific diagnostic criteria² but is instead based upon clinical history, laboratory findings, and imaging results. In 1965 the Schumacher criteria for the diagnosis of multiple

sclerosis established, purely on the basis of clinical findings: there must be CNS lesions disseminated in space and time, and alternative diagnoses must be eliminated.⁸ The McDonald criteria were formed to bring more relevant MRI information for the basis of diagnosis and treatment. Originally established in 2001, they were revised in 2005 and again in 2010. With these criteria, diagnosis is made on the basis of clinical characteristics alone or in combination with MRI features.⁹ The conventional therapies for multiple sclerosis include methylprednisolone (for acute relapses), interferon-beta, and other medications.

Several factors have been shown to predispose people to multiple sclerosis. One study showed that low vitamin D level predisposes to multiple sclerosis.¹ Another study showed people who are smokers are more likely to get multiple sclerosis.¹

The symptoms seen in multiple sclerosis patients depend on the nerves that are attacked;¹ therefore, not everyone will have the same symptoms. Some people will display sensory nerve symptoms because those are the nerves that are demyelinating. Others will show motor symptoms because those neurons are affected. And in some people, the spine is affected because of demyelination in the spine, with symptoms that can present either unilaterally or bilaterally.¹

Some of the earliest symptoms can be tingling, numbness, pain, burning, or itching. These symptoms may occur in the arms, legs, trunk, or face, depending on which nerves are affected. Some people even have a reduced sense of touch. Other more dramatic symptoms can be changes in the visual field; nystagmus (involuntary, rapid eye movement), a symptom that may be either transitory or progressively evolve; double vision; and even a complete loss of vision. Other symptoms include weakness, spasticity, and slurring of speech.

The typical picture of multiple sclerosis is that of remissions when symptoms reduce, and it is felt that the disease is reducing its rate of attack. This can be followed by relapses, where new symptoms or evolving symptoms occur as the disease becomes active again. However, in some of

the newer studies, it is noted that the demyelination is continuing, even in periods that appear to be in remission.^{3,4,6}

Cannabinoids are useful in the treatment of multiple sclerosis. They can help improve motor function, reduce activated microglia, and promote remyelination of the spinal cord.^{10, 12} These compounds provide treatment beyond just symptomatic relief of pain and motor impairment.

With cannabinoid therapy, pain is reduced, followed by a reduction in spasticity, rigidity, and tremor.¹¹ Viral models of multiple sclerosis show a reduction of spasticity and tremor,¹¹ produced through cannabinoid receptor agonists THC and Win55,212-2¹², which is a synthetic compound that acts to stimulate cannabinoid CB1 receptors. However, there are also activities that are independent of cannabinoid receptors, using neither CB1 nor CB2 receptors. There appears to be a “CB2-like” receptor reacts with an endogenous cannabinoid palmitoylethanolamide. This activity can be blocked by CB2 receptor antagonists.¹³⁻¹⁵

It has been shown that spasticity can be reduced by blocking both the endocannabinoid membrane transporter and the hydrolysis of the naturally occurring cannabinoids.¹⁶ CBD can also reduce microglial activation, leading to reduced inflammation.¹⁶ The action of CBD blocks the membrane transporter, thereby increasing the amount of endogenous cannabinoid that is available to help reduce pain and spasticity.

CBD further acts as an antioxidant because of its biochemistry and its modification and modulation of cell signaling.¹⁸ Through the modulation of cell signaling, it reduces the self-sustaining cycles of inflammation and oxidative stress. These CBD activities are carried out through noncannabinoid receptors. CBD acts as a competitive inhibitor of adenosine uptake in both macrophages and microglial cells. Activation of A2A adenosine receptors¹⁹ has an immunosuppressive effect on these cells. It decreases the amount of TNF-alpha that is produced by the microglial cells and is proinflammatory.

CBD acts to reduce oxidative and nitrosative stress.¹⁸ This is

accomplished by reducing super oxide generation and blocking the activation of NF-kB, which would lead to the production of free radicals. It further blocks both the activation of iNOS and the proinflammatory signaling from activated microglial cells.²⁰ CBD decreases the production of NF-kB and prevents the activation of a signal transducer and activator of transcription (STAT), STAT-1, which are both inflammatory. It also increases the anti-inflammatory signaling through the STAT-3 pathway.

Neuropathic pain is believed to be derived from microglial activation in the spinal cord and brain. It continues and is aggravated by the proinflammatory cytokines that are produced, including interleukin-1 beta, IL-6, and TNF-alpha. When activated, these microglia generate more oxygen species and initiation factors that tend to continue the cycle.²¹

CBD helps control nociceptive inputs to the CNS, and, when these are blocked, neuropathic pain is reduced.²² CBD also decreases the expression of VCAM-1. VCAM-1 is an adhesion molecule, when you reduce its production then you reduce the number of monocytes and lymphocytes coming into the inflamed area. This helps to reduce further expansion of inflammation. These cells are part of the ongoing cycle of inflammation and neurodegeneration. CBD reduces the up-regulation of chemokines, such as CCL2 and CCL5. These compounds are produced from astrocytes and perpetuate the up-regulation of inflammation neurodegeneration. One of the most powerful effects of CBD is that it restricts immune-cell transmigration into the CNS.

In the TMEX-viral model of multiple sclerosis,²³ early treatment with CBD in the acute phase had broad application in controlling the disease. It prevented the development of motor abnormalities and the progression to a chronic phase. It also reduced microglia activation, thereby reducing inflammation, demyelination, and axonal loss. In the model of multiple sclerosis, CBD was also shown to decrease the production of proinflammatory cytokines IL-1 beta, TNF-alpha, IL-2, IL-6, IL-12, and IFN-gamma. CBD was shown to induce cell proliferation in the microglial cells;²⁸ it was further shown that it could modulate migration of the cells that create inflammation in the CNS, thereby reducing the number of new

immune cells recruited to propagate the inflammatory process. CBD reduces antigen presentation and that will reduce the number of activated proinflammatory cells. It also controls the number of new immune cells which are coming into the area. By these two mechanisms CBD helps reduce inflammation and damage to neurons.

CBD decreased adenosine uptake through A2A receptors, leading to a reduced release of VCAM-1.²⁵ When this release is reduced, the adhesion of lymphocytes to the endothelial cells is lessened, enabling the blood-brain barrier to stay intact and reducing the effect of high glucose on the endothelial cells, thereby reducing inflammation.^{23,25} This process reduces the leukocyte infiltration, further decreasing chemokine production,²⁶ and reducing symptoms.

This is part of the immune modulation that is provided by CBD.²³ It limits the recruitment of lymphocytes to the inflamed site and modulates the activity of astrocytes and microglial cells.²⁹ It also produces anti-inflammatory effects through its action on A2A receptors that both block and stop effects²³ on endothelial cells.

CBD will protect oligodendrocyte progenitor cells,³⁰ the cells that produce myelin, by preventing their destruction and enabling the body with a pathway to produce more myelin. The loss of oligodendrocytes is the hallmark of multiple sclerosis. CBD works to prevent damage from oxidative stress by protecting mitochondria and preventing damage to the endoplasmic reticulum. CBD has also been shown to replace the oligodendrocytes that are destroyed by the process of neuroinflammation.³¹ When the endoplasmic reticulum is stressed, the stress response will produce serine/threonine kinase (PKR), and eIF-2 alpha, which creates an increase in phosphorylation. This phosphorylation increase promotes the processing and production of protein in response to stress. When these are triggered, the integrity of the endoplasmic reticulum is disrupted, and apoptosis in the oligodendrocytes is induced.

There is some speculation from the MS Microbiome Consortium, a group of scientists looking into possible causes of multiple sclerosis,³² that

noted abnormal bacteria in the microbiome of multiple sclerosis patients that can alter immune function. There is an increase in Methanobrevibacteriaceae flora present in people with multiple sclerosis. This flora can cause an increase in immune activity and is greatly increased in multiple sclerosis patients with a depletion of bacteria that can suppress immune function.

As with other diseases, multiple sclerosis appears to have multiple mechanisms, triggers, predisposing factors, and possible explanations for the disease. From the research that has been done, CBD appears to be effective in treating the disease, especially when added early in the disease process. It provides activity through both cannabinoid and noncannabinoid receptors, and it is through this diversity that CBD can have a broad application for multiple sclerosis in treating symptoms such as pain, spasticity, and tremors. The greater application is in the modulation of oxidative stress and neurodegeneration, and it is in these areas that no present treatment exists that can provide those affects.

XII

Pain

Pain is a very complicated subject, made more so because of its subjectivity. When someone is in pain, we do not really know how much pain they feel, nor the severity or how long it has lasted. Pain is something that's been with us since the beginning of time, and it is something that we have struggled to effectively treat. Today we have many modalities and medications that we use to treat pain; unfortunately, many of these are addictive.

A whole segment of society is addicted to pain medications today, partially because we are only guessing at the nature of the pain. Because of the subjectivity and difficulty of knowing what each person is feeling, choosing the right treatment becomes even more difficult. Even pain scales are very subjective, as people find it difficult to express exactly what they are sensing and feeling. This, too, makes treatment difficult.

There are many types of pain, but we are mainly going to discuss two: inflammatory and neuropathic pain.^{7.8.24} The underlying mechanisms of these types of pain differ. Neuropathic pain⁴⁸ is frequently chronic, and the neurons in the brain or the peripheral nervous system become hypersensitized. These neurons then generate abnormal or prolonged impulses that increase the sensitivity to pain. Other types of pain include diabetic and cancer neuropathy, postherpetic neuralgia, brachial plexus lesions, fibromyalgia, and multiple sclerosis. Research shows that 40 percent of cancer patients have neuropathic-created pain.⁵⁷ Similar receptors are used to process noxious stimuli, including mechanical,

thermal, and chemical.

The use of cannabis has a very long history as a pain reliever.^{9,10} Its first recorded use was more than 5,000 years ago in Chinese society, when the Chinese physician Hoa-Gho described the use of cannabis for surgical anesthesia. Between 315 and 392 CE, cannabis was used in ancient Israel for childbirth.

Present treatment for pain is only effective in approximately 50 percent of patients.⁴⁸ Today, the most commonly prescribed medications for significant pain are opioids. These compounds are addictive. Much of the recent research has shown the cannabinoids are more effective and use a different mechanism,⁵⁴ as the cannabinoid receptors are on afferent myelinated A fibers. Pain transmission is carried through these fibers,⁵⁶ and, since there are fewer mu-opioid receptors, the opioids are less efficient in controlling the pain at the spinal-cord level.

Cannabinoids selectively suppress noxious stimuli in the spinal and thalamic nociceptors.¹¹⁻¹⁵ These help provide antinociceptive effects.¹⁻⁴ In animal models of nociceptive or different types of noxious stimuli, there have been many studies that show that cannabinoids are equal in efficacy and potency to opiates.⁵ Systemic administration of cannabinoids suppresses behavioral reactions to acute noxious stimuli and further reduces inflammatory pain and pain from nerve injury.

Much of this has been shown to be through CB1 receptors, helping to suppress nociceptive transmission.⁵ The receptors also act to decrease the perception of pain.⁴⁸ When pain is present, there is an up-regulation of CB2 receptors at the sites of nociceptive processing. There is also an induction of CB2 receptors when neuropathic pain is present.^{65,66}

Exogenous cannabinoids can act at peripheral, spinal, and supraspinal levels,⁵ and they are not limited to one point of activity. The inhibition of the enzymes FAAH and monoacyl glycerol lipase (MGL) can also inhibit the production of nociception.⁶ FAAH breaks down the endogenous

cannabinoid anandamide that is active at CB1 receptors. Monoacylglycerol is the enzyme that breaks down arachidonyl glycerol (2-AG) that is active at CB2 receptors. When either of these two compounds are increased, they can decrease nociception.

Many of the cannabinoids have a central action in the brain; some of the studies that have been done have injected these compounds into the intracerebral ventricular system. In these studies, the central action of these compounds reduced pain sensitivity. They were found to be active in the dorsal lateral periaqueductal gray,⁴⁹ the dorsal raphe nucleus, the rostral ventral medulla, the amygdala, and the lateral posterior and submedial regions of the thalamus. This is the area of input from a spinal thalamic pathway⁴⁸ associated with pain. They are also active at the superior colliculus and noradrenergic nucleus A5.¹⁶⁻¹⁸ All of these are central areas involved with the processing of pain. The descending adrenergic system is active in mediating peripheral effects of pain.^{19, 26}

When CB1 receptors are activated, the result is a mixture of pain relief and some psychotropic effects. This is one of the limiting factors of using CB1 receptor agonists. Since these are the receptors that modulate the psychotropic activity, this can limit the dosage range of the agonists.

Another place where the cannabinoids work is at the spinal level, where they decrease the spinal reflexes to noxious stimuli.²¹ The CB1 receptors in the spine inhibit C fibers and A-delta fibers.²² Research also shows an interaction between cannabinoid and opiate receptors. THC has been shown to increase the effectiveness of morphine, and, with this increase in effectiveness, a reduced dose can be used to control the pain. THC has been shown to act at kappa and delta opioid receptors⁴⁸ whose stimulation acts synergistically with opiates.⁶²

In the periphery, these compounds also work to control inflammation. The CB1 receptors decreased input from pain sensors. CB1 and CB2 agonists act in the periphery to decrease nociception²⁴ and, through this decrease, the input and perception of pain. CB2 receptors in the periphery

help reduce nociception. These receptors have no psychotropic effects,²⁴ but they act against both acute and persistent pain.²⁵⁻²⁹ They help to inhibit the release of proinflammatory cytokines and proinflammatory factors that affect nociceptive nerve terminals. They also stimulate mu-opioid receptors⁴⁸ and act to stimulate the release of the endogenous opioid beta-endorphins.⁴⁸⁻⁵⁰

CB2 receptors are on peripheral nerve fibers³⁰ and on the spinal cord.⁶³ Microglial activation is reduced through these CB2 receptors, and the immune response of the microglial cells contributes to neuropathic pain.⁶⁷⁻⁷⁰

When 5 mg of delta-9-THC was administered in a study, it decreased the ability to distinguish pain.³¹ In another study 0.022-0.044 mg per kilogram (kg) of delta-9-THC was given intravenously and was shown to increase the pain threshold.³²

Acute pain is typically managed with opioids today; however, these do not work effectively when the pain is related to nerve injury.⁴⁸ THC, on the other hand, is antinociceptive even after nerve injury.⁵⁴ Cannabinoids have also been shown to be effective in alleviating what is referred to as intractable pain syndrome.⁴⁸

Chronic pain differs from acute pain because of neural changes that occur within the affected fibers that tend to prolong the noxious stimuli.²⁴ Allodynia, a decreased pain threshold, occurs with a heightening of the painful threshold of the noxious stimuli referred to as hyperalgesia. This process is also referred to as the wind-up phenomenon.⁴⁸ Many studies show that cannabinoids are more effective than opioids at controlling this problem.

In several cancer pain studies where the cancer pain was felt to be moderately intense,³³⁻³⁵ 20 mg of THC was equivalent to 120 mg of codeine. This was also seen with the compound Sativex (nabiximol) when used in animal studies using an animal model of cancer.⁶⁴ In a

randomized placebo-controlled, graded-dose study, this compound reduced pain and improved sleep. The dosages were between 1 and 4 sprays per day or 6 and 10 sprays per day. The lower number of sprays produced the least side effects and the same efficacy.

In a study of multiple sclerosis that presented with neuropathic pain,³⁶ a dose of 10 mg per day decreased the intensity of pain and provided pain relief and improvement on a quality-of-life scale. Participants showed no changes in their functional ability. Significant muscle spasms often accompany multiple sclerosis, and studies indicate here as well that cannabis reduces the spasms. In addition, cannabis has been shown to halt the progression of multiple sclerosis, reducing neuropathic pain and correcting sleep disturbances.⁵⁵

Neuropathic pain in multiple sclerosis is believed to begin from an autoimmune encephalomyelitis.⁷³ Because of the issues with psychotropic side effects, CB1 receptor agonists have to be modulated.²⁴ These psychotropic effects limit the amount of CB1 receptor agonists that can be used; therefore, these compounds may not be completely effective for neuropathic pain or nerve injury pain.

CBD can help with this pain due to its interaction or agonism of 5-HT1A receptors.⁶⁹ CBD helps suppress the up-regulation of microglial cells. Research shows that cytokines produced by the microglia sensitize neurons.⁷⁴ It is also been shown that CBD is an antagonist of 5-HT-3A receptors, and that this activity helps with nociception and the control of emesis.

Cannabinoid receptors function through G protein coupled receptors³⁷⁻⁴⁰ with multiple differences in the subtypes of G protein receptors. When stimulated, some of these will cause pain reduction without psychotropic activity. Stimulating these receptors also does not cause motor dysfunction. There are different types of G-protein coupled receptors, some when stimulated will reduce pain and provide no psychotropic activity. Their activity will be controlled by their location, those in the basal ganglia and cerebellum will affect motor control. For

analgesia it would be those located in the periaqueductal gray, rostral ventral medulla, spinal cord, and peripheral nerves that modulate pain.⁴¹⁻⁴³ It has been seen in some studies that stimulation of some cannabinoid receptors may provide different functions on the basis of the allosteric structure of the compound used. It is speculated that it is these modifications in the structure of the molecules that enable it to interact with different G protein subtypes.

Research studies show that FAAH degrades anandamide, 2-AG, and N-arachidonyldopamine (NADA).⁴⁰⁻⁴⁵ When you block the activity of FAAH, this leads to an increase in analgesia.⁴⁶ When this occurs, there is an increase in anandamide, which is an agonist for CB1 receptors. This analgesia is seen in both acute and chronic pain and creates a blunted sensitivity to pain. Blocking the protein cellular transport mechanism also leads to an increase in anandamide and an increase in analgesia.

Some nonsteroidal anti-inflammatory drugs (NSAIDs) enhance CB1 receptor activity.⁵¹ Indomethacin, and fluribuprofen both act to inhibit FAAH.⁵² They also block cyclooxygenase-2 (COX-2) activity, which increases anandamide and 2-AG.⁶⁷ It is through these activities that these compounds provide some analgesia. The activity of COX-2⁵³ facilitates the inflammatory response and can increase neuronal death. Cyclooxygenase catabolizes anandamide and 2-AG. This leads to a reduction of analgesia and an increase in pain perception.

Migraines are a different kind of pain and are considered to be vasomotor headaches. This is based on their pulsatile nature, their presentation in crisis, their periodic occurrence, and, for many, a hemicranial distribution (occurs on only one side of the brain). They can be associated in some people with generalized sensorial hyperesthesia, some sensitivity to light or noise (or both), and, in some, nausea or vomiting (or both). When you look at the symptoms, several studies have shown that cannabis has antimigraine properties.⁵⁸ In several of the studies, cannabis was shown to have equal or better pain relief than the

present medications used to treat migraine, ergotamine and aspirin.⁵⁹

Diabetic peripheral neuropathy is also a form of neuropathic pain.⁶⁰ The microglia cells have a prominent role, yet cannabinoid receptors are present on some neurons and microglial cells. Studies have shown that, during the normal course of diabetes, when no treatment is enacted, microglial density increases around neurons. This is seen in the dorsal spinal cord and the thalamus. Phosphorylated p38MAPK is elevated, an indication of activation of microglial cells. In addition, a reduction of both CB1 receptors⁷¹ and FAAH leads to an increase in endocannabinoids.⁷²

CBD has been shown to attenuate the development of neuropathic pain. In a study of CBD dosages of 0.1 mg/kg, 1 mg/kg, and 2 mg/kg, the effects elicited by CBD were continued even after discontinuation of compound, and no modifications were made in the diabetic state. CBD can work and reduce peripheral neuropathy and neuropathic pain. When CB1 and CB2 receptor agonists were used, the antinociception was only present when they were given and did not last after they were stopped.

CBD suppresses both inflammatory and neuropathic pain.⁶¹ It has an interaction with and stimulates glycine alpha-3 receptors, and it interacts with the S296 in the third transmembrane domain. Active in the dorsal horn of the spinal cord, it also interacts with TRPV1 receptors⁶⁸ that assist with the spinal control of pain. It reduces the degradation of anandamide, which is a CB1 receptor agonist. It also helps reduce pain through its agonist of 5-HT1A receptors.⁶⁹

XIII

Nausea and Vomiting

The emetic reflex, which consists of nausea, retching, and vomiting, is a protective reflex occurring in many animals in nature, with some exceptions. The nausea and vomiting reflexes are both interwoven and parallel. Experimental animals have shown us that they are not the same system and are controlled separately.^{1,2}

Vomiting expels toxins from the upper gastrointestinal tract. Nausea and pain, on the other hand, are warning signs. Nausea usually results in the cessation of consumption of whatever it is you have eaten, and it causes an aversion to be developed in the future¹. The vomiting center in the brain stem is called the dorsal vagal complex. Located in the medulla, it is made up of three particular areas: area postrema (AP), nucleus tractus solitarius (nucleus of the solitary tract, or NTS) and dorsal motor nucleus of the vagus (dmnX).

There are multiple types of input and processing of emetogenic stimuli.^{1,3,16} These include visual, olfactory, and pain sensory inputs processed through the limbic system. The receptors and neurotransmitters for the system consist of GABA and its receptors (GABA-R), as well as the cannabinoids and their receptors, particularly the CB1 receptors.

Another input is visceral irritants, such as foods, medications, radiation, and cytotoxic drugs. These compounds provide input locally in the stomach and small intestines. From there, neurotransmitters and their receptors transmit the information to the brain stem and the higher centers in the CNS. The local input here can be from hydrogen ions (H⁺);

D2 dopamine receptors; histamine, through H1 receptors; and serotonin, through specific 5-HT₃ receptors. Cannabinoid input is through CB1 and CB2 receptors, and neurokinin or substance P input is through neurokinin-1 (NK1) receptors. Any of these activations from these compounds is then passed on to the chemoreceptor trigger zone. These inputs may also directly affect this zone.

The terminals of the area postrema has its own receptors and neurotransmitters. In this area, serotonin acts through 5-HT₃ receptors, dopamine through D2 receptors, histamine through H1 receptors, neurokinin or substance P through NK1 receptors, and cannabinoids through CB1 receptors. The information sent here is then passed on to the solitary tract (also known as the nucleus tractus solitarius), which has its own receptors and neurotransmitters. Similar to the ones in the area postrema, they consist of serotonin working through 5-HT₃ receptors, dopamine through D2 receptors, histamine through H1 receptors, neurokinin or substance P through NK1 receptors, and cannabinoids through CB1 receptors. The output signals from here are then transmitted to the DMNX.

The DMNX receives input from multiple areas: the solitary tract, the chemoreceptor trigger zone, the stomach, and the small intestine. It also receives input from the limbic system and higher centers, an input that comes from anxiety, memory, anticipation, and dread. The receptors and neurotransmitters transmitting these impulses are limited to GABA and cannabinoids through CB1 receptors.

Input from the cerebellum comes from the vestibular system through GABA and from cannabinoids through CB1 receptors. Sensory input feeds into this area, which is made up of visual stimuli, olfactory input, and pain, making it both a complex and very subjective input and interpretation.

Because of memory, anticipation, and visual and olfactory input, even the environment can contain triggers that will set off nausea and vomiting, and due to these factors of anticipation and memory, it has become one of the hardest areas to control. Anticipation of pain and nausea has been the hardest area to relieve in cancer patients receiving chemotherapy.

In review, the brain stem's neurotransmitters and receptors include

serotonin, dopamine, neurokinin or substance P, histamine, endorphins, acetylcholine, GABA, and cannabinoids. These are the compounds or mechanisms for vomiting. Nausea is more complicated and not so fully detailed.^{17,18}

The serotonin 5-HT₃ receptor antagonists work very well in acute vomiting. However, for nausea that is not acute, such as in delayed chemotherapy-induced nausea and vomiting (CINV) and refractory CINV (the nausea no longer responds to the medicines taken to prevent it), this remains a significant problem,³ because these are not controlled by 5-HT₃ antagonists.

Studies on experimental animals have shown that serotonin 5-HT₃ antagonists, and substance P and neurokinin at NK1 receptor antagonists will control emesis. To control nausea, though, it seems that modulating the dopamine D₂ receptors and cannabinoid receptors that affect CB₁ activity is effective. Increasing anandamide, which acts through CB₁ receptors, can also help control nausea. This has also been demonstrated by the use of FAAH enzyme blockers, which work by increasing the amount of anandamide that is available to act. It has been shown that these are all found in the areas of the brain that control emesis.¹⁹

Some of the most difficult issues with pain, nausea, and vomiting are around chemotherapy. These toxins are not removed from the body by vomiting and, as has been seen, are not self-limited.² The other very difficult problem is the anticipatory issues that occur after the first rounds of chemotherapy and before the next chemotherapy visit.³ Researchers have shown that nausea is the more prominent problem, and not so much the vomiting. Acute nausea and vomiting can occur within minutes to hours of the chemotherapy administration. It will usually resolve within the first 24 hours, and the intensity peaks after 5 to 6 hours. The next form is delayed nausea and vomiting, which can develop more than 24 hours after the demonstration of the chemotherapy agent. It can peak at 48 to 72 hours and may last as long as 6 to 7 days.

Breakthrough nausea and vomiting occurs despite prophylactic treatments. It requires some form of rescue therapy, and it may be acute or

delayed. Refractory nausea and vomiting occurs in chemotherapy cycles despite prophylaxis and may also be seen when rescue therapy fails in earlier cycles.

The first major step for the physician is to control the vomiting. The serotonin receptor subtype of 5-HT₃ receptors is specific to this problem, and experimental research has shown that an antagonist for the 5-HT₃ receptor can prevent acute retching and vomiting.^{1,4-8}

The 5-HT₃ antagonists have been combined with corticosteroid dexamethasone in human studies, demonstrating that this combination can reduce acute vomiting in 70 to 90 percent of patients.^{2,9-15} This combination does not work, however, for delayed nausea and vomiting and has been shown to be ineffective for breakthrough, refractory, and anticipatory nausea and vomiting.

This is where researchers have shown that the cannabinoids are helpful. It is the CB₁ receptor activity that helps to reduce emesis. This has been shown experimentally for delta-9-THC. In addition, CB₁ agonists or inverse agonists will increase vomiting.²⁰

Delta-9-THC works at receptors in the area postrema and the nucleus of the solitary tract,^{20,22} blocking the serotonin 5-hydroxytryptophan (5-HTP) receptor. Lower doses act centrally, and higher doses of 10 mg/kg act peripherally.²²

CB₂ receptors in the brain stem can contribute to antiemesis. 2-AG will affect both CB₂ and CB₁ receptors and helps to prevent emesis.²⁴ FAAH inhibitors alone, or those added to anandamide, prevent emesis induced by morphine-6-glucuronide.^{24,25} The research suggests that this happened through the CB₁ receptors.

In research done on the ferret, some of this antiemesis was produced through TRPV₁ receptors.²⁵ Also noted are the endocannabinoids anandamide and NADA, both active at CB₁ and TRPV₁ receptors.²⁶ This research has led to the discovery of other avenues and receptors through which our endocannabinoids function.

Research has also shown that our cannabinoid system interacts with

other neurotransmitter systems, in particular the definite interaction with 5-HT system.²⁷ The cannabinoids interact with both CB1 and 5-HT3 receptor in the dorsal vagal complex.^{28,29} Both anandamide and synthetic cannabinoids inhibit 5-HT3 receptors.³⁰ Delta-9-THC has been shown to inhibit 5-HT3A receptors,³¹ an innovation that is noncompetitive and binds at an allosteric site on this receptor.³¹ This inhibition is not through direct interaction with the receptor but from its interaction at a different site.

CBD is a special case with low affinity for both CB1 and CB2 receptors.³² In a rat model for nausea, at a low dose of 5 mg/kg, it inhibits vomiting and anticipatory retching.³³⁻³⁶ As with other studies of CBD, there is a biphasic activity, and at a high dose of 20 to 40 mg/kg, it will potentiate vomiting.^{33,34} Doses up to 20 mg/kg had no effect on 2-AG-induced vomiting.³⁷ This activity was not through CB1 receptors. Agonists of 5-HT1A receptors reduced serotonin's availability,³⁰ suggesting that through this mechanism, CBD controls nausea and vomiting.

CBD at 5 mg/kg suppresses vomiting by blocking 5-HT1A receptor antagonists and reducing the rate of neuronal firing and the levels of forebrain serotonin.³⁹ CBD also appears to be an allosteric inhibition of 5-HT3 receptors.⁴⁰ CBD also inhibits the reuptake of an anandamide,¹ which provides CB1 receptor activation and was shown to inhibit the breakdown of anandamide, which further increases its level and activity.¹

As we've said previously that nausea is more difficult to control.⁴¹ Using 5-HT3A antagonist can stop emesis, but there will still be activity in area postrema.⁴² In the studies done in rats, they do not vomit but have a series of reactions that are felt to be the equivalent of nausea,¹⁶ including gaping, chin rubbing, and paw treading. This pattern is also seen in animals before they vomit.⁴³ When linked to a stimulus, this pattern is referred to as conditioned gaping. It has been shown that delta-9-THC prevents

condition gaping from occurring,⁴⁴ because of blocking blocked by CB1 receptor antagonists or inverse agonists.^{45,46} It is also been shown that, by preventing the breakdown of anandamide, this will also block conditioned gaping⁴⁷ because this is a CB1 receptor agonist.

Research also shows that CBD reduces nausea by a non-cannabinoid mechanism. A dose of 5 mg/kg works to block nausea. This activity is carried out by serotonin receptors in the somatodendritic area by 5-HT_{1A} auto receptors that are located in the dorsal raphe nucleus. Nausea appears to be mediated by 5-HT receptors acting in the forebrain in an area of the insular cortex.⁴⁸

Anticipatory nausea develops over the course of repeated chemotherapy.⁴⁹ Whenever an event recurs, it produces more nausea, vomiting, or both. This is best understood as a classic conditioning response.^{16,50} Control of anticipatory nausea is best at the time of conditioning or at the time of re-exposure to the conditioned stimulus.¹⁶ Giving 5-HT₃ receptor antagonists at the time of chemotherapy can prevent the formation of anticipatory nausea.^{16,49} In addition, studies have shown that delta-9-THC prevents conditioned retching¹⁶ and conditioned gaping.

CBD has also been shown to prevent anticipatory nausea^{16,35} at a dosage range of 1 to 5 mg/kg.^{16,51} At this dose, it prevents conditioned gaping and retching. At doses of 5 to 10 mg/kg, it prevents conditioned retching, but at doses of 20 to 40 mg/kg, it increases vomiting.^{1,46} Since CBD also inhibits FAAH enzyme activity, it elevates the level of anandamide^{16,51} and will prevent conditioned gaping.

Neuromodulation that is effective in controlling emesis is through the serotonin 5-HT_{3A} receptors and substance P and neurokinin at NK1 receptors.³ In summary, the most effective neuromodulation to control nausea is through control of dopamine D₂ receptors and cannabinoids at the CB₁, CB₂, and 5-HT_{1A} receptors.¹⁶

XIV

Arthritis

The presence of arthritis implies that there is inflammation in one or more joints.² Symptoms can be joint pain, stiffness, tenderness, locking, and a crackling noise referred to as crepitus. When the joint is inflamed, it can be swollen from an effusion of fluid. Arthritis has many causes and forms, and most forms worsen with age. The two most common forms are osteoarthritis and rheumatoid arthritis.

Osteoarthritis¹ is the most common form of arthritis and affects the synovial joints.²⁵ Also referred to as degenerative arthritis, degenerative joint disease, and degradation of joints, the articular cartilage will be eroded and appear soft, frayed, and thinned. The arthritis is actually not limited to the joint and articular surfaces, as inflammation can extend down into the subchondral bone, the bone to which the cartilage is attached. It is seen mainly in weight-bearing joints, such as the knees and hips, but it has also been known to affect the hands, feet, and spine. While the exact cause of osteoarthritis is unknown, we believe that hereditary and developmental abnormalities can predispose a person to the disease. In some cases, there is evidence of metabolic disturbances and mechanical wear and tear on the joint itself.

Examination of the joint will show erosion of the cartilage, even to the extent that bony surfaces are exposed. Inflammation can spread into the adjacent bone. This erosion of cartilage and exposure of the bone leads to pain that in turn leads to reduced range of motion and then muscle atrophy and lax ligaments.³ The leading cause of chronic disability in the

United States,⁴ more than 27 million people are affected with osteoarthritis.

Rheumatoid arthritis is a chronic, systemic inflammatory disorder²⁵ that can lead to deformed joints that are painful and have lost function. The joints themselves are warm and tender, with increased stiffness early in the morning. This arthritis most commonly affects hands, feet, and the cervical spine, but it can also affect shoulders and knees. Just as in osteoarthritis, the causes are not understood.⁶ With rheumatoid arthritis, we see an inflammatory response of the synovium, the capsule around the joint. There is swelling of the synovial cells, an excess of synovial fluid, and, over time, the development of fibrous tissue in the synovium called the pannus. There is also an erosion of the underlying bone, and thinning and destruction of the cartilage.⁶

In rheumatoid arthritis, inflammation can also affect other organs,⁷ such as the pericardium (the lining around the heart), the pleural (the lining around the lungs), and the whites of the eyes. There can also be subcutaneous manifestations of inflammation, referred to as nodular lesions.

Both forms of arthritis are involved with inflammation, which is at the core of the disease itself. The form and extent of the inflammation varies with the disease, but, in both types of arthritis, we see immune system activation as a prominent feature. Both also have the loss of articular cartilage. The loss of cartilage is mediated through several modalities.⁹ Proinflammatory cytokines, such as IL-1, IL-6, and TNF-alpha are involved,²⁵ as well as chemokine IL-8, nitric oxide, and prostaglandin E2 (PGE-2). We also see proteases, one of which is metalloproteinase, and aggrecanases, such as disintegrin and metalloproteinase with thrombospondin (ADAMTS)-4 and -5. It also involves some anti-inflammatory compounds, such as IL-10 and TGF-beta.²⁵ These are the components—cytokines, chemokines and proteases—that lead to the destruction of cartilage. It is through control of these that an intervention can stop and prevent cartilage demise. Once the destructive process begins,

immune cells are recruited that then are activated, and the inflammation may spread down through the cartilage, causing destruction of the subchondral bone.

Cannabinoids have been shown to reduce inflammation and prevent cartilage destruction. They are also capable of reducing nociceptive or sensory processing of the pain and thus help to reduce the pain perception that is associated with arthritis.²⁵ Cannabinoid agonists prevent the production of IL-1A,¹⁰ one of the most potent destructive compounds of the cartilage. IL-1A induces proteoglycans and collagen degradation. It blocks the production of PGE2 and its activity on the chondrocytes. The chondrocytes are the cells that build cartilage; they have both CB1 and CB2 receptors. These help inhibit the activation of NFkB, a transcription factor that can modulate inflammation and compounds related to nitric oxide production. The cannabinoid agonists inhibit the expression of iNOS, prevent COX-2 activity, and block the activation of NFkB. These compounds stop the breakdown of articular cartilage.

CBD has also been shown to block the progression of osteoarthritis and rheumatoid arthritis in both mouse and rat models.^{11,15} In a murine study where a chemical is injected to cause an acute arthritis and in chronic relapsing collagen-induced arthritis CBD will reduce symptoms of both types. When the dose was given intraperitoneally (injected into the peritoneum), the optimal effective amount was 5 mg/kg per day. When the dose was given orally, the optimal effective dose was 25 mg/kg per day. Both lower and higher doses were tested, and none were as effective as these optimal doses.

The murine studies showed that CBD reduced the production of collagen specific antibodies, reduced IFN-gamma production, and caused the suppression of lymphocyte proliferation. This suppression of lymphocyte proliferation was a general one, as the stimuli that usually lead to proliferation caused by mitogens or chemicals were suppressed. Even specific antigens—lipopolysaccharides from gram negative bacteria—which usually cause activation, did not induce the proliferation. These are two of the main types of activation that can lead to inflammation and

introduce lymphocyte proliferation and activation.

CBD was also shown to decrease TNF-alpha production and the production of reactive oxygen bursts. It was also shown to inhibit cytotoxic T-cell activity. It suppressed the function of macrophages and their ability to present antigens, thereby reducing the number of activated immunocytes and thus the amount of inflammation. CBD further helps to reduce inflammation by modulating the production of TNF. It helps to reduce the production of IL-1 and IFN-gamma. Studies indicated that CBD further reduced the amount of a chemokine, IL-8, that was produced by B cells. These results were not strain specific.^{11,15}

Studies also noted that in the acute form of arthritis, the mice treated with CBD had complete resolution. Those with the chronic form did not have complete resolution but did have a reduction in joint damage by 70+ percent. These studies clearly indicate that there is a dose-dependent suppression of both arthritis and joint damage with CBD.^{11,12} Part of this activity is through immunosuppression, which leads to a shift away from T-helper 1 response, considered an inflammatory response. Part of the anti-inflammatory activity of CBD is the reduction of the concentration of TNF-alpha in the synovium. It also reduces ROS that can increase inflammation and tissue damage. CBD also blocks nitric oxide production by the macrophages, which stimulates further inflammation. Through this process of immune modulation, CBD helps to inhibit inflammatory cell migration and infiltration into the tissue.^{12, 13} Among the largest cells inhibited through migration and infiltration are the neutrophils.

CBD further reduces oxidative stress by reducing the production of ROS^{12, 14} In this process, CBD helps reduce free radicals by blocking the activation of NADPH oxidase. CBD reduces the amount of TNF-alpha that is secreted and reduces the activation of p38MAPK. The result of these activities is a reduction in the spread and continuation of inflammation.

CBD has been shown to influence chondrocyte precursor cells. These mesenchymal stem cells¹⁶ showed increased survival and migration to the site of tissue injury. CBD also led to chondrogenic differentiation from the mesenchymal stem cells. This process leads to the prevention of cartilage

destruction.^{11, 16-20}

Through his research, John McParland came to the conclusion that “the forces of embryogenesis become the forces of healing after birth.”²¹ He is referring here to the influence of the endocannabinoid system on fibroblasts. His work showed the extensive involvement of the endocannabinoid system in skeletal tissue repair.

Research shows that cannabinoid-based medicines²² can help reduce pain with movement and pain at rest, as well as improve the quality of sleep. The pain reduction was from a suppression of the disease itself, along with a reduced perception of pain.

Cannabinoid receptor agonists reduce fibroblast-like synoviocytes (FLS) in both osteoarthritis and rheumatoid arthritis to reduce the production of IL-6 and IL-8²³, a proinflammatory cytokine and a proinflammatory chemokine, respectively. Reducing these is one avenue that some cannabinoids effect, thereby reducing the production of inflammatory cytokines. The reduction also helps reduce the propagation of inflammation and arthritis itself and can help prevent the destruction of cartilage.

Experiments showed that IL-6 and IL-8 were not blocked by CB1 or CB2 receptor agonists; therefore, this activity is independent of cannabinoid receptors. The cannabinoid agonists were independent of TRPV1 receptors and PPAR-gamma receptors and reduced IL-6 production in nonstimulated cells. The reduction was not shown for IL-8.

These are all of the receptors that have been documented to lead to the actions of cannabinoids. This information and these studies point to other methods of activity, perhaps through unknown cannabinoid receptors or mechanisms of which we are not presently aware.

IL-6²⁵ is the main driver of inflammation in rheumatoid arthritis. It induces osteoclast differentiation and leads to bone destruction and resorption. Endocannabinoids contribute to the regulation of bone mass.²⁶ This modulation of bone mass is important in arthritis because of the destruction of the bone under the cartilage. We might surmise that it's

important as well when dealing with osteoporosis and osteopenia. Since cannabinoids help modulate bone density, this may provide another application for them.

The regulation of bone mass is felt to be modulated through the CB2 receptors present on both osteoblasts and osteoclasts. Research shows that CB2 receptor antagonism reduces osteoclastogenesis²⁴ and can be accomplished through the antagonism of both CB1 and CB2 receptors. With this activity, there is reduced formation and function of osteoclasts, the cells that break down bone. In the collagen-induced murine version of rheumatoid arthritis, the cannabinoids reduced the amount of inflammatory cytokines that were present. They also decreased antibody production, and, when begun early in the inflammatory process, they inhibited the formation of acute arthritis and reduced the amount of bone destruction.

The endocannabinoids are not limited to AEA and 2-AG. Other cannabinoids are seen in the tissues that do not react with cannabinoid CB1 or CB2 receptors and are referred to as “entourage” compounds.^{27,28} Two of these compounds, OEA and PEA, are found in the joint but do not help modulate the endocannabinoid system through traditional receptors. PEA has anti-inflammatory activity through the PPAR-alpha receptors.²⁹ These receptors account for some of the entourage activity. They also help modulate nuclear transcription factors that help control metabolic processes and reduce inflammatory reactions. In a study looking at the tissues and synovial fluids of patients with osteoarthritis, rheumatoid arthritis, and normal joints, they were tested and compared. In both osteoarthritis and rheumatoid arthritis, AEA and 2-AG were found in the synovial fluid but not in normal synovial fluid. PEA was lower in osteoarthritis and rheumatoid arthritis than in normal joints.

The decrease in PEA may reflect the contribution of it to the disease process in osteoarthritis and rheumatoid arthritis. The progression of these diseases could be related to the loss of PEA through reduced production or degradation.

2-AG levels were lower in rheumatoid arthritis than in osteoarthritis in

the synovial fluid. However, there was no difference in the levels found in the synovial tissue of the joints. Is there an imbalance in the production of cannabinoids that leads to the production and continuation of joint inflammation? Looking at the differences in the levels of endocannabinoids present in arthritic joints versus normal joints and the differences between rheumatoid arthritis and osteoarthritis, it seems plausible that variance in endocannabinoids presence reflects a problem.

Research shows that CB1 and CB2 receptors are coupled in some way to TRPV1,³⁰ and that linkage may be related to their activity. We are confident that the coupling is linked to the vasodilation effect in blood vessels in the knee joints. These are complicated interactions, though, not fully understood at this time. The issues with inflammation are further complicated by the regulation of cannabinoid receptor expression.^{31,32} The receptor expression varies depending on the nature of the inflammatory stimulus and the tissue that is involved. When inflammation occurs, some tissues increase the number of cannabinoid receptors and other tissues reduce the number. Cannabinoid receptors appear to down-regulate in inflamed joints, which may be related to an up-regulation of stimulants, anandamide, 2-AG, or all three. Research shows that prolonged exposure to these compounds leads to some cannabinoid receptors being withdrawn back into the cells.^{33, 34}

In summary, research indicates that the whole process of arthritis is linked to inflammation in complex ways. While the cause of these diseases is not completely known or understood at this time, research shows us that the cannabinoid compounds can be very helpful in reducing the inflammation, free radicals, nitric oxide, and immune-cell infiltration and activation. Given these outcomes, we believe further research and investigation into the application of these compounds is necessary and may result in CBD being one of the front-runners for the control of inflammation and pain that is related to arthritis.

XV

Cancer

Cancer is one of the most common diseases and killers today. Causes are numerous and may be biological, environmental, viral, or bacterial. There are also genetic predispositions to cancer; however, when you look at the broad majority of cancers, the cause is really unknown. This would include, among many others, breast, colon, rectum, lymph nodes, uterus, bladder, pancreas cancer, bone marrow, and stomach.¹

Some of the most common and recognized environmental exposures that cause cancer are tobacco, polycyclic hydrocarbons, asbestos, arsenic, and vinyl chloride. These agents have been proven to be carcinogenic, and precautions have therefore been put into place for people who are exposed to them. Other physical agents that are carcinogens include ionizing radiation, ultraviolet radiation, and aflatoxin B1.

The next group of causes is viruses, many referred to as oncogenic because they can start and cause cancer. These viruses transform cells into a neoplastic state. This occurs when the cell is not a natural host. In a natural host, they are replicated and released. When the cell is nonpermissive (does not support the replication of a virus's mutant gene), the virus then takes control of the replicating process and the cell becomes neoplastic. The viral DNA can be inserted into cellular chromosomes; once inserted, the proteins for viral proliferation are produced. Viruses have both early and late proteins, and the viral genes also help maintain the transformation. The retroviruses are the most well-known of these oncogenic ribonucleic acid (RNA) viruses. They carry their own reverse transcriptase so they can convert their RNA into deoxyribonucleic acid

(DNA), which can then be incorporated into the cellular DNA and be replicated. These viruses carry three genes: group-specific antigens, internal structural proteins, and envelope proteins.

One of the subtypes of these RNA retroviruses is the human T-cell leukemia virus (HTLV), either type I or type II. Another virus in this category is the human immunodeficiency virus (HIV), also referred to as lentivirus. Infection with this virus also predisposes the individual to other opportunistic infections.

Oncogenic DNA viruses include papovavirus, simian virus 40, adenoviruses, herpes viruses, Epstein-Barr virus, hepatitis B virus, hepatitis C virus, human papilloma virus (HPV) type 16 and 18, and human herpes virus-8 (HHV 8) (also known as Kaposi sarcoma-associated herpes virus, or KSHV). These viruses have DNA, and they can directly insert it into our cellular DNA.

Bacterial causes of cancer include the *Helicobacter pylori*. This bacterium can cause gastritis and lead to ulcers and cancer formation. Other bacteria can cause cancer, but they have not been as well studied as *H. pylori*.

In our normal cellular DNA, we have the precursors for cancer development. We have oncogenes and proto-oncogenes, both of which can be activated through replication. These are matching homolog's two retroviral oncogenes. There are no introns, the segments that begin replication in retroviral oncogenes; these segments get changes from proto-oncogenes if and when they become associated. Proto-oncogenes produce very specific compounds that can be growth factors, growth factor receptors, or signal transducer proteins and are known to function in normal cells. We also have tumor suppressor genes that control autophagy and apoptosis.¹ Produced modulators of the cell cycle called cyclin proteins help modulate the speed of cell cycles. Cyclin-dependent kinases are compounds that stop the cell cycle between G1, the resting phase, and S phase, which is for DNA synthesis.

Some human cancers are known to be derived from proto-oncogene. These include Burkitt's lymphoma, chronic myeloid leukemia, bladder carcinoma, some lung and colon carcinomas, and neuroblastoma. These have all been shown to be derived from the activation of normal proto-

oncogenes.¹ In some cases cellular proto-oncogenes convert to oncogenes. When this occurs their activation forms cancers. They can be produced from genetic translocation, promoter insertion, point mutations of the DNA, and delusional mutations and amplification.¹

We all carry the potential to develop cancers in our DNA. When our immune system is functioning normally, these cancers are immediately destroyed. However, when the immune system is not functionally normally, these cancers can escape detection and destruction.

Epigenetics is the study of cellular changes that occur but are not related to changes in the DNA and is another area that addresses the occurrence of cancer.² Epigenetics describes cellular potential for change and a response to changes in the environment that can modulate DNA translation and reflects the cells' unlimited potential. Every cell in our body has the same DNA, but the expression of that DNA is unique to each cell, tissue, and organ. It is the epogenome that aids in turning off and on of particular genes in particular tissues. For example, the DNA in our hair, eyes, and fingernails are all the same except that different genes are turned on and off, giving them individual characteristics. Part of the epigenome activity is through biochemical modification that include methylation and the histone wrapping of DNA. These two categories of modifications turn genes on and off. This whole process changes with age, and the number of times a cell has divided will affect its susceptibility to cancer. The more cells divide, the more likely we are to develop inflammation and have reduced stem-cell vitality and ability to repair damage.²

Cancer is very prevalent throughout the world, with the highest prevalence in North America, where it is estimated that 1.5 percent of the population greater than 15 years old has or will have cancer. That calculates to about 3.2 million individuals affected. In Western Europe 1.2 percent of their population 15 years of age and older, or 3.9 million individuals, is affected, and in Japan it's 1 percent of their population.

The basic treatments for cancer include surgery, radiation therapy, and chemotherapy, and then follow-up that is determined by the type of cancer that is treated. Our basic treatments of cancer are not very successful; side

effects from radiation therapy and chemotherapy are devastating by themselves. Cancer treatment is often a process of trying to kill the cancer before you kill the person.

Cannabinoids and their potency as anticancer agents has been researched mainly outside of the United States. The reason for that is current US government's policy on marijuana and the government's need to show that there is no medical benefit to marijuana. For this reason, only certain types of cancers have been studied and many others not.³² Cannabinoids are potent anticancer agents because they modulate many of the key signaling pathways, including growth, differentiation, angiogenesis (the growth of new blood vessels), and metastasis.

Some tumors are very susceptible to cannabinoid-induced growth inhibition.^{4,32,33} These include lung carcinoma, glioma, thyroid epithelioma, lymphoma, leukemia, skin carcinoma, uterine carcinoma, breast carcinoma, prostate carcinoma, neuroblastoma, colorectal cancer. Through the manipulation of growth and its inhibition, cannabinoids can reduce tumor bulk and metastatic disease.

Cannabinoid activity with possible antitumor functions includes modulation of adenylyl cyclase activity in the modulation of intracellular c-AMP. Another factor that can contribute to antitumor activity is the modulation of protein kinase A (PKA) a protein kinase pathway. This pathway modulates Ca²⁺ and K⁺ channels and can modulate neurotransmitter release. Other pathways also can affect cell fate. These include stimulation of the MAPK pathway, extracellular-signal-regulated kinase (ERK), which is similar to and functions with the MAPK pathway, and then stress-activated kinases. The stress-activated kinases can contribute to cell growth, differentiation, autophagy, and apoptosis. They can also affect the phosphoinositide 3-kinase (PI3K)-Akt survival pathway. Control of this pathway can contribute to cell survival or cell death. Stress-activated kinases can also stimulate ceramide production de novo, meaning the natural cellular production, not by outside stimulation. This ceramide production can activate other stress proteins and lead to the loss of mitochondrial function.

The cannabinoids have been shown to induce apoptosis of tumor cells while protecting normal cells from any damage. Cannabinoids inhibit the growth of transformed cells and prevent the tumors from angiogenesis. They also are capable of inhibiting the metastasis of cancers and growth factor receptor signaling.

In endothelial cells, which are the cells that produce blood vessels, cannabinoids control their size, their ability to differentiate, and their permeability. Cannabinoids prevent endothelial cell migration and cancer cell migration,^{33, 40} inhibit cell adhesion, prevent invasion of surrounding tissues, and inhibit the cancer's ability to metastasize. Cannabinoids also decrease the life of the endothelial cells, making them mature quickly and become impermeable.

Much of the activity that the cannabinoids carry out is through a known group of receptors.^{34, 35} These include cannabinoid receptors CB1 and CB2, TRPV1,³⁶ putative cannabinoid receptors, the orphan G-protein coupled receptor 55 (GPR55),³⁷ and the PPAR-gamma and 5HT1A receptors.³³ In worldwide research, these are the most common receptors that have been shown to interact with cannabinoids, but many actions that are seen with these compounds must be carried out by other receptors or other methods that we are not aware of presently.

The effects of these compounds vary with the type of cancer cells with which they interact. Each cell type has its own susceptibility or resistance to the cannabinoids. Different receptors are used in different cell types, and in some tissues the activities are independent of receptors. CBD is the most potent cannabinoid used against cancers. It has no psychotropic effects and has a very low toxic profile. We will now look at some of the cancer types that respond well and see the mechanism of action and exactly what happens in most cell types.

Gliomas are one of the most difficult cancers to treat.⁴ Even with the best radiological, surgical, and chemo therapies, the median survival is less than one year.¹¹ The first report of the use of delta-9-THC was reported in 1998. It was shown that THC was very active against gliomas,¹² and that

this was not mediated by CB1 receptors.³³ There was partial CB2 receptor activity that decreased proliferation of the glioma cells. It was further shown that this activity was not carried out through TRPV1 receptors, but that the THC generated ROS in the tumor cells, which led to their death.³³ An elevation in ceramide production was also noted. There were two peaks of elevation—one happening within minutes with a two-fold increase in ceramide, and the other seen days after the treatment with a four-fold increase. It was later learned that the ceramide elevation in the second peak was due to de novo synthesis of ceramide, which increased the production of stress-regulated protein p8. The elevation of p8 leads to the activation of proapoptotic pathways.¹³⁻¹⁶ In addition, the injection of cannabinoids into the gliomas prolonged the individual survival and completely eradicated tumor in 20 to 35 percent of the treated animals in studies.¹³

Further studies of gliomas showed that the cannabinoids exerted control over cell proliferation and survival pathways. In controlling the ERK-1 and ERK-2 pathways, they decreased proliferation, cell migration, and invasiveness.^{5,33} They also exerted control over the PI3K/Akt pathway,^{8,33} which can also decrease proliferation, reduce migration, and eliminate invasion. CBD was shown to decrease the activity of 5-lipoxygenase and thus decrease proliferation, migration, and invasion.

CBD was also shown to decrease the amount of FAAH, which is the enzyme that degrades our common endocannabinoids. With this action, there is an increase in anandamide, which stimulates the CB1 receptors. The combination of CBD and anandamide decrease the proliferation, migration, and invasion by cancer cells. It increases the production of ROS in tumor cells, as well as decreases cellular glutathione, which makes the tumor cells more sensitive to oxidative stress, and triggers apoptosis or autophagy.

Cannabinoids affect the focal adhesion kinases⁹ that affect a cancer's ability to grow and spread. Inability to grow and spread will stimulate an increase in oxidative stress and the production of free radicals. The free-radical increase will lead to an increase in activation of caspase-9 and -8.

The activation of these two compounds increased and activated caspase-3, leading to mitochondrial dysfunction. This mitochondrial dysfunction will in turn lead to a leaking of the cytochrome c into the cytoplasm from the mitochondria, with an additional reduction in the membrane potential of the mitochondria, leading to a collapse in energy production.

These compounds decrease the production of hypoxia-inducible transcription factor 1 alpha (HIF-1alpha).^{33,45} With the decrease in this compound, a cell has difficulty in responding to hypoxia and oxidative stress, which contributes to a decrease in proliferation, migration, and invasion. In these studies, it was shown that cannabinoids selectively affect tumor cells and do not affect normal brain cells.^{17,18} They actually have been shown to protect normal neurons. In some studies, the stimulation of CB2 cannabinoid receptors were shown to induce tumor regression.¹⁹

In many studies CBD was chosen over THC because of its nonpsychotropic effects, and in some of the earliest ones, CBD was shown to inhibit human glioma cells.²⁰ This inhibition was dose-dependent, led to apoptosis, and was accomplished through the induction of overwhelming oxidative stress.^{18,37,41-44} These studies also showed that CBD led to depletion of glutathione from the tumor cells. This induction of ROS-stimulated apoptosis could be reversed through the antioxidant tocopherol.³⁷ All the activities of CBD were independent of the known receptors.²⁰

CBD was shown to increase the release of cytochrome c from the mitochondria into the cell cytoplasm. The activation of caspases-8, -9 and -3 led to the activation of both the intrinsic and extrinsic apoptotic pathways. In essence, this happens because of CBD's ability to disrupt mitochondrial function, leading to the activation of the intrinsic pathway and disruption of nuclear and other cell functions to activate the extrinsic pathway. This is further assisted with the down-regulation of signaling molecules for tumor cell proliferation.^{33, 45} These proliferation pathways include ERK and PI3K/Akt. With the blocking of these pathways, the cells' ability to respond to stress and proliferate is reduced. The hypoxia-

inducible transcription factor is blocked as well, which reduces the cells' ability to respond to the hypoxia and increase free radicals. A couple of studies showed that combinations of CBD with THC causes cellular death at lower doses than either one was capable of causing by itself. This was accomplished through cell-cycle arrest and increased production of ROS. The cell death was accomplished through the sustained activation of caspases -3, -7, and -9, which assist in the breakdown of mitochondrial function.

THC was shown to increase intracellular accumulation of ceramide through de novo synthesis. This process leads to apoptosis, and ceramide levels are inversely correlated with malignant progression in glial tumors and poor prognosis.²¹ With increased levels of ceramide, there is increased expression of the P8 transcription factor, thus inducing endoplasmic reticulum stress and the production of activating transcription factor 4 (ATF4) and cyclophosphamide, doxorubicin, Oncovin (vincristine), and prednisone (CHOP). These two stress compounds increase the activation of pseudokinase tribbles homolog 3 (TRB3). This compound converges on the mitochondria to trigger the intrinsic pathway to apoptosis. This is combined with the activation of the caspases.¹⁶

Multiple cannabinoids acting through CB1 receptors can down-regulate pathways and growth factors that reduce tumor cells' ability to survive.²² These pathways are activated by some cannabinoids independent of receptor activity. In their endeavor to grow and expand, all cancer cells must have new blood-vessel growth and migration ability.⁴ At first they must grow locally, then spread locally with the potential for metastasis to distant sites. Angiogenesis is required for this whole process to occur, and angiogenesis requires the proliferation and migration of endothelial cells, the ability to manipulate the extracellular matrix, then the morphologic differentiation of the endothelial cells to form tubes. Multiple factors are required in the proper timing and sequence for this to occur.

Cannabinoids inhibit angiogenesis, which also enables them to metastasize.^{22,23} These compounds change the blood-vessel morphology and control pathways that modulate the activity of new vessel formation.

They reduce the production of vascular endothelial growth factor (VEGF), and the production and activation of the VEGF receptor. In doing so, cannabinoids can then control the formation and activity of new blood vessels. They further inhibit the migration of vascular endothelial cells.²⁴ This activity inhibits cell migration of the endothelial cells and reduces their survival. Success in accomplishing this depends on the CBD dose: lower doses stop migration while a larger dose is necessary to produce apoptosis.²⁵ CBD's activity helps to further regulate the expansion through other tissues.

CBD down-regulates the expression of tissue inhibitors of metalloproteinases (TIMPs).^{26, 27} The metalloproteinases are compounds that enable cells to break down the intercellular matrix and are needed for both expansion of the tumor cells and the invasion of blood vessels. Through this control of TIMPs, CBD controls tumor growth, angiogenesis, and metastasis. Tumors cannot expand if they cannot degrade the extracellular matrix.

CBD causes the release of apoptotic enzymes and the cleavage of cell surface receptors. It decreases tumor-cell proliferation, migration, adhesion, and dispersion, which in turn prevents the tumor from growing and spreading beyond the limits when CBD is started. By preventing new blood-vessel formation and increasing the host defense mechanisms, CBD further enhances the destruction of the tumor. With the inhibition of angiogenesis this is accomplished through the inhibition of endothelial cell migration and survival, when you cannot produce functional endothelial cells for blood vessels then there is no cell migration or survival.²⁸⁻³¹

The cannabinoids alter gene expression. They protect the development of glioma-derived stem-like cells. By supporting and controlling these cells, cannabinoids help to create proliferation of glioma cells and to modulate their differentiation into the forms that are needed. They reduce glioma tumor-cell proliferation, one of the cancers that is suspected to be stem cells.⁴ The tumors suspected of derived from stem-cell duration include gliomas, and hematopoietic, breast, and prostate tumors.

Breast Cancer

In 2006 Ligresti et al. showed that CBD potently and selectively inhibited breast-cancer cell growth⁴⁸ and reduced infiltration of lung metastasis. Their work showed that this was accomplished through TRPV1 receptors and CB2 receptors through indirect activation by way of FAAH.⁴⁹ They also showed the induction of oxidative stress. Through the activity modulated through the receptors, CBD blocked cell proliferation, invasion, and metastasis.

Of the cannabinoids tested, CBD was the most effective at suppressing breast cancer, and it was shown to down-regulate the ID-1 gene.⁴⁹ The ID-1 gene is what controls the invasiveness of breast cancer and its ability to metastasize. By blocking this gene, CBD prevents proliferation of breast cancer, and the migration and invasion in surrounding tissues. CBD was also shown to mediate up-regulation of extracellular signal-regulated ERK.^{33, 42} This control led to increased ROS and further reduced cell proliferation. CBD also reduced primary tumor mass and the number of metastatic foci.

Tests demonstrated that CBD was active against both estrogen-positive and estrogen-negative breast cancer.^{33, 43} The activity of CBD was independent of CB1, CB2, and TRPV receptor activation and did not affect normal nontumor cells. The CBD induced both autophagy, which is the recycling of normal cell constituents, and apoptosis. The activities of autophagy and apoptosis remediated through increased endoplasmic reticulum stress from inhibiting Akt/mTOR/4EBP1 signaling. This increases ROS, which in turn reduces the cells' ability to compensate for these compounds. A reduction in mitochondrial membrane potential then leads to the reduction of energy production for the cancer cells.

The mitochondrial decline is marked by the translocation of Beclin-2 and its interaction with mitochondrial proteins, and the introduction of Bid into the mitochondria itself. There is leakage through the mitochondrial membranes, and holes are punched that allow the release of cytochrome c into the cytoplasm. This activity activates the apoptotic pathway, also known as the suicide pathway. If you inhibit the activation of

the caspases, this would lead to reduced apoptosis. However, with this reduction there was a rebalancing and an increase in autophagy. This modulation was carried out by Beclin-1. CBD increases the cleavage of Beclin-1.^{50, 51}

Through this cleavage, there was an increase in the cleavage of Bid and this was translocated into the mitochondria. The movement of Bid into the mitochondria creates further leakage of cytochrome c from the mitochondria into the cell cytoplasm. This loss of cytochrome c leads to a failure in the production of energy in the cancer cells, and they can no longer survive.

The Beclin-1 cleavage leads to fragments being translocated into the mitochondria.^{33,43,50,51} These fragments lead to cytochrome c leakage and trigger apoptosis. The combination of these processes leads to a decrease in cancer-cell proliferation and all activity that would support cell life. In this stress state and with the genes turned off, there can be no invasion or metastasis.

Leukemia and Lymphoma

Leukemia and lymphoma are immune-system tumors, and the immune system is heavily favored with CB2 receptors,⁵³ making these tumors some of the most responsive to cannabinoids. In early studies CBD was shown to induce apoptosis by the activation of caspase-3 through a CB2 receptor activation^{33,52} CBD also caused activation of caspase-8 and -9 in response to its ability to create free radicals in the cancer cells, leading to apoptosis and reduced proliferation. The Bid present in the cells was fragmented, and some of those fragments were transported into the mitochondria, which led to reduced mitochondrial membrane potential. With this there was no longer an efficient electron transport, leading to a reduction in energy production and an increase in free-radical generation. This was also accompanied by leakage of the cytochrome c from the mitochondria into the cytoplasm. With this release of cytochrome c from the mitochondria leading to a breakdown in mitochondrial function, more ROS was created. CBD also reduces levels of p38MAPK,⁵² which leads to a reduction in cell

differentiation and further apoptosis.

Studies demonstrated that immune cells were much more sensitive to CBD than to THC. For THC to be effective, a concentration of 10 micromoles or greater is needed to induce apoptosis in immune cells. This was accomplished by the activation of caspase-2, -8, -9, and -10. Through this activation, the intrinsic pathway was activated from mitochondrial damage. In the cytoplasm, Bid cleaved, with fragments being transported in the mitochondria, leading to the leakage of cytochrome c into the cytoplasm.

THC also led to an increase in ceramide. This increase led to a loss of mitochondrial membrane potential, which created a loss of cellular energy and the leakage of cytochrome c into the cytoplasm. It also produced phosphorylation of Raf-1, mitogen-activated protein kinase-1 (MEK-1) and -2 and ERK-1 and -2. The phosphorylation of these compounds leads to an increase in the development of apoptosis.

The combination of these activities leads to the decrease in proliferation and invasion of the immune-based cancers. Due to the high receptor concentrations for cannabinoids, the response to CBD was quick, and, in the studies, low concentrations of CBD were very effective.

Lung cancer

Studies of lung cancer showed that CBD reduces the invasiveness of the cancers.⁵⁴⁻⁵⁶ The activity included CB1, CB2, and TRPV1 receptors and an up-regulation of tissue inhibitor of MMP-1. The up-regulation of TIMP1 led to decreased invasiveness and decreased angiogenesis. With this in place, it was difficult for the lung cancers to inlarge and to metastasize.

The increase in TIMP1 was induced by a couple of mechanisms. The induction of p38MAPK and an increase in ERK both led to an increase in the amount of TIMP1 that was produced and greatly limited lung cancer's ability to change the matrix and send out new blood vessels to increase its size. Also shown was a reduction of plasminogen activator inhibitor-1 (PAI-1). This compound is critical to invasion by the cancer cells. Blocking PAI-1 reduced the cells' ability to spread and take over more tissue.⁵⁵

CBD at concentrations as low as 0.01 to 0.05 micromoles/liter, 1×10^{-6} was able to decrease metastasis up to 84 percent. This study showed both the effectiveness of CBD and the low doses at which it can be used for treatment.

Colon Cancer

The study of colon cancer has been done in animals and is induced by the compound azoxymethane (AOM).⁵⁷ This compound induces aberrant cryptic foci and polyps, followed by tumor formation. This model exactly reflects human colon cancer. Cannabinoids induced up-regulation of phosphor-Akt, iNOS, and COX-2. This regulation system starts the modified ROS production. It prevents free radicals, thereby reducing the formation of precursors to colon cancer. There was a down-regulation of caspase-3.⁵⁶⁻⁵⁸

Studies with CBD at the dosage of 1 mg/kg showed reduced aberrant cryptic foci formation. At a dose of 5 mg/kg, polyps and tumors were reduced. In this animal model, CBD was shown to be capable of both the treatment of the cancer and prevention of the formation of cancer.⁵⁷⁻⁵⁸

The dose of 1 mg/kg reversed the protective effects of phosphor-Akt. It also reversed the activity and protection of caspase-3, which led to an increase in free radicals in the mitochondria and the destruction of the mitochondria itself, leaving the tumor cells without energy.⁵⁸

A comparative study between CBD and delta-9-THC showed that, used in combination, they had a greater effect at a lower dose. It was shown that this combination helped reduce iNOS but did not affect COX-2.⁵⁷

2-AG, which provides stimulation of CB1 receptors, also increased. This stimulation helps provide more antiproliferative effects. Anandamide, which acts at both CB1 and TRPV1 receptors, increased as well. Part of this increase was due to the blocking of the enzyme FAAH, which breaks down anandamide and some 2-AG.⁵⁸

It was shown that CBD protected normal cells and the cells' DNA from oxidative damage. There was no genotoxic damage from the CBD, and CBD reduced intestinal contractility. The other effect of CBD is reduction

of intestinal inflammation.^{57, 58}

Studies show that it is the combination of CBD and THC that is the most effective in treating colon cancer. Most of the research that has been done has been carried on outside of the United States because of the status of marijuana in the United States. There are now companies that are producing synthetic cannabinoids, which are being studied and used under the funding of the drug companies.

Our knowledge of this whole endocannabinoids system must include the understanding that it is the balance in cell activity that is required for health, and too much or too little leads to dysfunction of the systems. The activity of the cells affected by this imbalance will depend on the cell type. The receptors found in the cells will influence their responsiveness or resistance to cannabinoid treatment.

It has been my goal to highlight some of the research that has been done and demonstrate that this research shows that marijuana does have medicinal effects. Closing our eyes to this leads only to the ill health of our population. It is my hope that science and true scientific discovery will override the prejudices that exist at this present moment. There is much that can be done and will be done in the future. My only hope is that we are participants in this discovery process, which is actually only the rediscovery of a true gift that has been given us for our health.

Summary

I hope this book has provided you with some insight and information into the benefits of medicinal cannabis. Based on only a fraction of the research that has been completed, we have outlined the various benefits and described their method of action for some diseases. Cannabinoids act through many mechanisms using many different receptors. Their activity is both central and peripheral, each cannabinoid having its specific range of benefits.

It is time to remove our blinders, release our prejudices, and focus on the benefits that are offered for so many diseases. It will be through further research that we will tease out the actual pathways and benefits for each cannabinoid. Eventually, it will be the combinations of multiple cannabinoids that will give us the greatest benefits.

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Glossary

Acetylcholine—an acetic ester of choline, used by some neurons as a neurotransmitter.

Adenylate cyclase/ adenylyl cyclase—the activity of this compound is inhibited by the stimulation of cannabinoid receptors, this leads to their activity and responses in the cells when these receptors are used.

Adjuvant—an additional therapy to enhance or extend the primary therapies effects.

Afferent nociceptors—a peripheral nerve organ which transmit information to the brain about pain or injury.

Agonism—a compound that stimulates a receptor and produces a reaction, such as stimulating a drug receptor and causing the same reaction.

Akt/mTOR/4EBP1—this is a signaling pathway that helps regulate the cell cycle, this is used by cancer cells to aide survival, when it is blocked the cells loose ability to adjust and control their survival.

Alpha-synuclein—a protein that is found at the ends of neurons, function not fully understood, in Parkinson's disease it is seen to fold and therefore cannot be removed or broken down; it is believed to be involved in dopamine release and uptake.

Analgesia—reduction of pain.

Antagonism—opposition in action to structures, agents, physiologic processes, neutralize, create a different or block the action of an agonist.

Antigens—cell surface markers which are specific to each cell, they can induce a state of sensitivity and/or immune responsiveness.

Anxiolytic—an action or compound to reduce anxiety.

Astrocytes—one type of glial or supportive neuroglial cells.

Autophagy—consumption of a cell from its own digestive components.

Basophils—a granulocyte with basic staining granules, in blood and tissues, contains inflammation activating substances.

Beclin 2—a protein associated with cell death from autophagy, it is moved from the cytoplasm into the mitochondria and help to trigger autophagy.

Beta amyloid—a specific type of amyloid protein, composed of linear nonbranching fibers, formed into sheets and plaques, with hyperphosphorylation and forming an inflammatory reaction from astrocytes and microglia.

Bid—is a protein product which when transported into the mitochondria it helps trigger autophagy.

Bradykinesia—a decrease in spontaneity or movement.

Cannabinoids—organic substances present in Cannabis sativa, having a variety of pharmacological properties.

Cannabinoid receptors—also inhibit N—and Q-type calcium channel activity, which controls calcium entrance into the cells; they stimulate potassium (K⁺) channel conductance, allowing more potassium into the cells.

Cascade—a sequence of interactions, once initiated continues until completed, each interaction is activated by the preceding one.

Caspase 3—a protein that begins a cascade of enzymes that lead to cell apoptosis or cell death.

Chemokines—a chemical which is used to attract other cells.

Chemotactic—movement of cells in response to chemicals, or complement factors moving toward higher concentrations.

Cholinergic—nerve cells or fibers that use acetylcholine as their neurotransmitter.

Complement System—a group of heat-labile components in the serum, they can be destructive to certain bacteria and other sensitized cells which have been marked with complement-fixing antibody. C is a group of approximately 20 distinct serum proteins, these interact through enzymes and produce cleavage of cell membranes. They are designated from C1 through C9; subunits are designated by letters a, b, etc.

Complex II—a series of enzymes in the mitochondria that help convert food to energy.

Cryptic foci—abnormal areas within the colonic crypts, pitlike depressions in the colonic surface.

Dendritic cells—immune cells that process and present antigens to effector immune cells, located in lymph nodes.

Dopaminergic denervation of the striatum—when these cells no longer provide dopamine stimulation then the areas where these neurons affect they no longer have the dopamine stimulation, this greatly affects movement.

Dopaminergic neurons—nerve cells or fibers that use dopamine as their neurotransmitter.

Down-regulation—to reduce production, activity.

Eicosanoids—physiologically active substances derived from arachidonic acid.

Endothelial cells—flat cells which line blood vessels, lymphatic vessels and the heart.

Endotoxin—a bacterial toxin which is not released into the surrounding medium, it remains on the bacterial cell wall.

Eosinophils—a subtype of leukocytes, found in the blood and tissues, usually associated with allergies and parasitic infections.

Equilibrative nucleoside transporter 1—a protein that encodes for a

membrane glycoprotein that transports nucleosides from the surrounding medium, found in cell and mitochondrial membranes.

ERK pathway—extracellular signal regulated kinase, when activated will lead to apoptosis or cell death.

Excitotoxicity—the process of exciting cells and then poisoning them; leads to nerve injury and death.

Exocytosis—the process of a cell excreting its secretory granules from inside the cell to the outside environment.

Extracellular Matrix—the components outside the cells that supports the cells.

Fibrillar species—referring to the non-digestable fibrils formed in Alzheimer's disease.

Fibroblast—a stellate or spindle shaped cell with cytoplasmic processes present in connective tissues, capable of forming collagen fibers.

GABAergic neurons—gamma-aminobutyric acid, a calming or inhibitory neurotransmitter, stimulation of GABA reduces activity in the neurons.

Globulins—family of proteins that circulate in the blood, some are precursors to active compounds and others are immunoglobulins for protection, divided into alpha, beta and gamma.

Glucocorticoid—any steroid-like compound capable of influencing intermediary metabolism and of exerting an anti-inflammatory effect; cortisol is the most potent naturally occurring compound in our bodies.

Homolog's to retroviral oncogenes—our oncogene DNA segments are identical to retroviral oncogene and proto-oncogenes, the belief is that the retroviral genes were incorporated into our DNA.

HPA—hypothalamic-pituitary-adrenal axis—plays a pivotal role in our response to stress, preparing the body for fight or flight.

hyperesthesia—a condition with an abnormal increase to sensitivity of sensory stimuli.

hypoacetylation of H3 histones—the huntingtin protein in the abnormal form binds to the DNA and prevents some gene information from being transcribed, this is accomplished by reducing the acetylation of some H3 histones bound to the chromatin.

Hypoxia-inducible transcription factor—when cells are living in reduced oxygen this transcription factor is activated to help the cells adapt to low oxygen, CBD prevents this protective process from occurring.

Intercalated nuclei—a cluster of neurons in the amygdala, when inhibitory tone is reduced there is an indirect reduction in anxiety by their effect on the central amygdala.

Intracytoplasmic inclusion bodies—a conglomeration of proteins which have accumulated inside the cell and cannot be removed or broken down.

Leukocytes—immune system cells, typically present in lymph tissue and the blood; there are 3 different types depending on their origin: myeloid, lymphoid and monocytic.

Ligand—a molecule that binds to a specific receptor.

Lymphocytes—white blood cells, derived from lymph tissue, circulate in the blood, two types. B and T, which are involved in our immune protection.

Macrophage—a monocytic cell which lives in the tissues, they function to engulf and take in inert substances and bacteria; participate in immune function through presentation of antigens to lymphocytes and secrete various immune modulatory compounds.

MAPK cascade—mitogen activated protein kinase—these are involved in helping the cell to respond to different stimuli or stressors, help regulate cell proliferation, gene expression, differentiation, mitosis, cell survival, and apoptosis.

Mast cells—mainly reside near small blood vessels, activation effects the permeability of blood vessels, activity increases with immune function.

Matrix Metalloproteinases—an enzyme that breaks down proteins, its

action is dependent on incorporating a metal, zinc, or cobalt.

Mineralocorticoid—one of the steroids of the adrenal cortex that influence water and electrolyte (sodium and potassium ions) metabolism and balance.

Monocyte—a leukocyte with one large nucleus, circulates in the blood, spleen, lymph nodes, and loose connective tissue.

Monomeric—only having a single component.

mu-opioid receptors—one of three types of opioid receptors.

N-acetyl aspartate—derived from the amino acid aspartate, which has been acetylated, second most common compound found in the brain.

Neoplastic—abnormal tissue that grows by cellular proliferation more rapidly than normal and continues to grow even after the initiating stimulus has ceased, structure and function is different from normal tissues and usually form a distinct mass.

Neural progenitors—these are the stem cells which can produce neurons, or have the potential to become nerve cells.

Neurogenesis—formation of the nervous system, stimulating the production of neurons.

Neuromodulatory function—any compound that can affect the activity of the brain, as in changing the effects of neurotransmitters (either their release or functional activity).

Neutrophilic—pertaining to neutrophils which are mature immune cell from the granulocytic series, also known as inflammatory cells.

Neutrophils—mature white blood cells, found in the blood and can move into tissues.

Nigrostriatal dopaminergic neurons—efferent neuron connections between the substantia nigra and the striatum, they use dopamine for their neurotransmitter.

Nitrosantive—to reduce a nitrosyl free radical.

Nitrosive stress—increased production of nitrosyl free radicals.

Nitrosylated—a free radical formed from nitrogen and oxygen bonded together.

NK cells—specialized immune cells that kill cancer cells and protect against intracellular infections by viruses, parasites and bacteria.

Nocioceptive—capable of appreciating or transmission of pain.

Oligodendrocytes—one of the three types of glial cells, the other two being astrocytes and microglia, along with neurons these cells make up the central nervous system; these produce the sheet-like processes which are wrapped around individual axons to form the myelin sheath; these protect the axon and speed up the neural transmission speeds.

Oligomeric—a compound with a few repeating units.

p38MAPK—mitogen activated protein kinase which is activated by cell stress and cytokines, they are involved in apoptosis (cell death) autophagy self-destruction by the cell itself and cell differentiation.

Palmitoylethanolamide—another endocannabinoid which is derived from fatty acids, it participates in the entourage effect, does not bind to CB1 or CB2 receptors.

Paternal transmission—this is passed through the father's genes.

Pathogenesis—the pathologic, physiologic, or biochemical mechanism resulting in the development of a disease or morbid process.

Paw treading—rubbing pads of forelimbs, this is a sign of nausea which is seen in rats.

Phosphorylation—addition of a phosphate to an organic compound.

Phospholipids—a lipid containing phosphorus, including lecithins and other Phosphatidyl derivatives, the basic components of biological membranes.

Phytocannabinoids—plant derived cannabinoids, not synthetic.

PolyQ forms—aggregates of huntingtin protein, normally they are soluble and in Huntington's disease they are insoluble.

Present antigens—antigen presentation—some subtypes of immune cells

will engulf the intruder and then process it; when this is complete the cell will then display the specific antigens to effector cells and then they will produce antibodies to attack the antigens on the invader cells; this can be accomplished through direct cell activity, antibodies which are released and by the complement system.

Protease—an enzyme that breaks down proteins/polypeptide chains.

Pyrogen—any agent that can cause fever.

Raf-1—also known as RAF proto-oncogene serine/threonine-protein kinase, proto-oncogene c-RAF, c-Raf it is part of the MAPK pathway, help regulate growth and cell division.

Retrograde diffusion—this moves in the opposite direction that nerve impulses are traveling, moving backwards across the synaptic cleft between two neurons.

S296 in the third transmembrane domain—this particular is a domain in glycine receptors in the spinal cord where CBD exerts some of the reduction in neuropathic pain, this reduces the nociceptive input for pain perception.

Senescence—the state of being old.

Somatodendritic—a particular site on the body of neurons in the substantia nigra pars compacta, these have neuromodulatory effects on nausea.

Striatum—collective name for the caudate nucleus, putamen and the globus pallidus.

Striatal atrophy—loss of neurons in the striatum.

Substantia nigra—a group of nerve cells in the brain stem.

Substantia nigra pars compacta—a group of nerve cells in the brain stem that use dopamine as their neurotransmitter and are involved in reward, addiction and movement.

Superoxide dismutase—an enzyme that converts 2 oxygens and 2 hydrogens into hydrogen peroxide and oxygen.

Synovial cells—cells which make up the synovial membrane of a joint.

Tau protein—a protein that associates with microtubules and other elements of the cytoskeleton; found in the plaques of Alzheimer's disease.

THC—tetrahydrocannabinol, delta-9-tetrahydrocannabinol.

T-Helper 1—Th1 cells—a specific set of T lymphocytes that function in cell mediated immunity, these are CD8 lymphocytes and NK cells, these cells attack viruses, cancer cells and cells where invaders are inside and replicating, these are the cells that create chronic inflammation.

Thromboxanes—a group of compounds in the eicosinoids, related to prostiglandinws, they influence platelet aggregation, clot formation and an oxygen containing 6 member ring.

Transmembrane amyloid precursor proteins—proteins residing in a position through the cell membrane, these precursors can be converted into amyloid proteins; which cannot be dissolved by the enzymes.

Tumor Necrosis Factor-alpha—main cytokine for beginning and propagating an inflammatory response, activates immune cells and causes degranulation of other immune cells, causing the increase of inflammation.

Tyrosine hydroxylase—the enzyme that converts the amino acid l-tyrosine into L-DOPA.

Ubiquitin-proteasome system—a group of enzymes that provide protean breakdown for disposal.

Up-regulation—to increase production of molecules.

Vasoactive amines—influence the tone and caliber of blood vessels.

VCAM-1—this is an adhesion molecule which attracts and encourages more inflammatory cells to enter the area.

Vesicle—a closed structure surrounded by a single membrane.

About the Author

An international lecturer, author, and pediatrician, **Dr. John Hicks** has practiced integrative medicine for over thirty-five years. With an innovative approach to chronic disease, Dr. Hicks uses objective laboratory analysis to individualize medical and nutritional support, applying progressive and proven treatments to the physical and emotional well-being of each patient.

In recent years, Dr. Hicks has been recognized as an authority on medicinal cannabis and its application to a wide range of chronic illnesses and diseases. His focus has centered on the human endocannabinoid system and how cannabidiol—better known as CBD—provides powerful anti-inflammatory modulation, helping patients who suffer from dysfunction of their immune and nervous systems. He lectures around the country on medicinal marijuana, and specifically on the use of CBD.

Dr. Hicks graduated from the University of Louisville School of Medicine and spent two decades with a traditional pediatric practice in the Midwest before shifting his focus to holistic medicine. He is the author of numerous articles for a variety of health journals, including the *Autism Science Digest*, *Health Wise*, and others. Additionally, Dr. Hicks was a contributing author to the books *Cutting Edge Therapies for Autism* and *Bugs, Bowels, and Behaviors*.

Dr. Hicks lives in Los Gatos, CA with his wife and stepdaughter. He is the founder and medical director of Green Health Medical Group, a private practice focusing on holistic pediatric and family medicine. More information about his work can be found at www.johnhicksmd.com. For

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