

# BALANCE IN HEALTHCARE



**James David Adams**

**Bentham Books**

# **Balance in Healthcare**

Authored by

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## **Balance in Healthcare**

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ISBN (Online): 978-981-4998-96-3

ISBN (Print): 978-981-4998-97-0

ISBN (Paperback): 978-981-4998-98-7

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## **PREFACE**

Balance is a traditional concept. When you live in balance, your body heals itself. This used to be common knowledge. We need to relearn balance. Balance is a concept that used to be taught and practiced in the family. A positive, encouraging family can help us reach our best potential.

Diet is critical to balance. Many people in the modern world eat diets that emphasize meat and processed foods. Fruit, vegetables and traditional foods are being ignored. The body needs a balanced diet to keep the guts healthy. Insoluble fiber from fruits and vegetables are necessary for gut health and for the health of the immune system.

Toxic lifestyles have become normal in the modern world. Regular daily exercise is considered nonessential. Exercise is critical to health because muscles need exercise in order to make myokines that maintain the health of the heart, brain, kidneys and other organs. Obesity has become normal in the modern world. Visceral adipocytes secrete inflammatory proteins called adipokines that cause heart disease, type 2 diabetes, osteoarthritis and promote cancer.

The immune system includes the Peyer's patches in the gut which are sites of maturation of many immune cells. Macrophages, T cells, B cells and dendritic cells in the Peyer's patches are critical to immune defenses against bacteria, viruses and fungi introduced into the gut. Gut health is compromised by alcohol, obesity, nonsteroidal anti-inflammatory and other drugs.

The endocannabinoid system derives from arachidonic acid. Prostaglandins, thromboxanes and other arachidonic acid metabolites are in balance with endocannabinoids to regulate pain, inflammation and other processes. Endocannabinoids and prostaglandins are made where they are needed and have very short half-lives. Diet, chronic pain and other lifestyle factors can alter the endocannabinoid system.

The antioxidant system depends on vitamin E, vitamin C, glutathione and other factors that protect the body from oxygen radicals and other radicals. The vitamins come from food. Glutathione is made in every cell of the body. Diet and lifestyle can alter the antioxidant system.

There is an energy balance in the body that depends on ATP, cAMP, NADPH, NADP, NADH and other factors. These factors protect DNA, mitochondria, proteins and lipids that are vital for cell repair and survival.

Spirituality is neglected by the modern approach to healthcare. Balance is included in spirituality in some religious beliefs. Spirituality is a choice we can make and can help promote our mental and physical health.

### **CONFLICT OF INTEREST**

The author declares no conflict of interest, financial or otherwise.

### **ACKNOWLEDGEMENTS**

Declared none.

### **CONSENT FOR PUBLICATION**

Not applicable.

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## **Balance and Lifestyle**

**Abstract:** The world is facing a crisis of overpopulation that is confounded by the toxic lifestyles that people choose. The healthcare community must treat the diseases these toxic lifestyles cause, such as heart disease, type 2 diabetes, arthritis, and cancer. Living in balance can prevent and cure these diseases. The public should know more about balance and how to keep the body healthy.

**Keywords:** Arthritis, Balance, Cancer, Exercise, Heart Disease, Stress, Toxic Lifestyle, Type 2 Diabetes.

### **1. INTRODUCTION**

Balance is a traditional concept that is central to healthcare. Living in balance involves staying thin and strong, being of service to others, having loving relationships with family members, being kind and respectful to other people, and being spiritual [1, 2]. Traditional healers teach that when the body is in balance, it heals itself. It is easy for a doctor to decide if a patient is in balance. The blood pressure, blood glucose, and blood cholesterol are normal.

The modern world is centered around the need to make money. Education focuses on helping people learn how to have lucrative careers. Many people assume they must be aggressive to succeed in their careers. This may add to the stress. Stress is responsible for decreasing balance.

Diet is critical to balance [1, 2]. Many people in the modern world eat diets that emphasize meat and processed foods. Fruit, vegetables, and traditional foods are being ignored. The body needs a balanced diet to keep the guts and the immune system healthy since the immune system has a large component in and near the guts. Insoluble fibers from fruits and vegetables are necessary for gut health and for the health of the immune system.

Toxic lifestyles have become normal in the modern world that leads to obesity [3, 4]. Toxic lifestyles can include alcohol abuse, drug abuse, sexual abuse, obesity, smoking, lack of exercise and other possibilities. In some parts of the world,

obesity is a sign of wealth and success, whereas being thin is a sign of poverty. Regular daily exercise is considered nonessential. Exercise is critical to health because muscles need exercise in order to make myokines that maintain the health of the heart, brain, kidneys and other organs. Obesity has become normal in the modern world. Visceral adipocytes secrete inflammatory proteins called adipokines that cause heart disease, type 2 diabetes, osteoarthritis, and promote cancer.

## **2. LIFESTYLE AND LONGEVITY**

The Framingham studies and several other studies have shown the effects of toxic lifestyles on health and longevity [5, 6]. These are studies of several thousand people followed over many years.

1. Smoking, high blood cholesterol, high blood pressure and obesity increase heart disease and decrease life expectancy.
2. Smoking cessation can increase life expectancy.
3. Exercise and elevated HDL levels decrease the risk of heart disease and increase life expectancy.
4. High blood pressure increases the risk of stroke. An enlarged left ventricle, as seen in congestive heart failure, increases the risk of stroke. These factors decrease life expectancy.
5. Never smoking, eating a healthy diet, vigorous daily exercise, maintaining low body weight, and limiting alcohol consumption increase longevity and decrease the risk of developing heart disease, type 2 diabetes, and cancer.
6. 90% of diabetes, 80% of heart disease, 70% of mortality from heart disease, and 50% of mortality from cancer have been attributed to living with toxic lifestyles [6].
7. Processed foods, especially processed meats, increase the risk of developing cancer, according to the World Health Organization.
8. Red meat consumption greatly increases the risk of several intestinal cancers [7].
9. Alcohol consumption increases hypertension [8]. Women have a lower risk of developing alcohol induced hypertension than men. Black people have a higher risk of developing alcohol induced hypertension than whites and Asians. Alcohol consumption damages the guts and can dose dependently increase the risk of cancer [6].

The addition of any aspect of a toxic lifestyle decreases life span and increases the risk of developing heart disease, type 2 diabetes and cancer. These toxic lifestyle aspects include smoking, eating an unhealthy diet, avoiding exercise, obesity and

drinking more than 2 alcoholic drinks daily [6]. These toxic aspects are additive in terms of decreasing longevity and increasing disease.

### **3. HEALTHY DIET**

A healthy diet, as defined in the studies discussed here, is described by the alternate healthy eating index [8]. The current recommendations are to eat vegetables, fruit, nuts, soy protein, more white meat than red meat, cereal grain, more polyunsaturated fats than unsaturated fats, multivitamins, and no more than 2 alcoholic drinks daily. Eating a healthy diet is associated with less disease [9].

However, eating too much of a healthy diet can cause obesity. Obesity decreases longevity and increases the risk of type 2 diabetes, heart disease, arthritis and cancer [6]. On the other hand, being too thin also decreases longevity by about 20 – 25 years [6]. Anorexia causes hypoglycemia, damages the heart and is associated with depression, bipolar disorder, and suicide [10].

For many people, weight loss involves eating less and exercising more [1, 4]. Weight control should become a lifestyle change and should be incorporated into normal life. Dieting without exercise tends to cause loss of muscle tissue. Fad diets are used by many people, usually with limited success. One such diet is the ketogenic diet, which emphasizes eating fat and protein while eliminating carbohydrates. This diet may be useful in the treatment of cancer [11]. However, fibroblast growth factor levels increase during a keto diet [12], which stimulates cell growth, perhaps even cancer growth.

The modern diet is partly the result of wartime rations from World War 2. Some types of processed meat, processed cheese and nonwhole grain flour were promoted for wartime use. Cigarettes were also given in rations to soldiers. Now, these wartime foods are being weaponized against the population as a whole and are greatly decreasing general health. High fructose corn syrup and other flavor enhancers are being added to foods to increase sales. Fat contents of foods are kept high to increase sales. High sugar and high-fat contents cause the release of endorphins and enkephalins in the brain resulting in food addiction [4]. In addition, endocannabinoids are released in the body after high fat and high sugar meals resulting in pleasure and increased appetite [4]. People are choosing to eat more food than is needed for optimal health, resulting in obesity.

The modern diet contains obesogens, which are compounds that stimulate appetite. Many of these compounds stimulate sterol regulatory element binding protein (SREBP). Stimulation of SREBP induces several lipogenic genes responsible for the accumulation of fat and stimulation of appetite. Examples of

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## **Spirituality and Balance**

**Abstract:** Most religions teach moderation, which is the balance between excess and deficit. Moderation leads to happiness and good health. Spirituality can teach people to be moderate and motivate people to maintain healthy lifestyles. The Chumash Indian Religion is discussed in detail since balance is an essential component of the religion.

**Keywords:** African, Buddhism, Christianity, Chumash, Confucianism, Hinduism, Islam, Moderation, Sacred Medicine, Taoism.

### **1. INTRODUCTION**

Patients with chronic diseases are frequently advised to make lifestyle changes such as exercising more and getting rid of excess weight. Healthcare professionals may be less likely to recommend adding spirituality to lifestyle changes. A recent study found that patients with chronic diseases seek more spirituality in their self-management [1]. This spirituality can be good, such as adding inner strength. Spirituality can also negatively affect patients who experience inner battles, feelings of guilt and becoming a victim. Spiritual leaders should be ready to counsel patients experiencing negative effects.

### **2. CHRISTIANITY**

Balance is a concept that appears in most religions. Balance is discussed several times in the Bible. Ecclesiastes 3 describes the process of balance in the world. “For everything, there is a season, and a time for every matter under heaven: a time to be born, and a time to die; a time to plant, and a time to pluck up what is planted; a time to kill, and a time to heal; a time to break down, and a time to build up; a time to weep, and a time to laugh; a time to mourn, and a time to dance; a time to cast away stones, and a time to gather stones together; a time to embrace, and a time to refrain from embracing; a time to seek, and a time to lose; a time to keep, and a time to cast away; a time to tear, and a time to sew; a time to

keep silence, and a time to speak; a time to love, and a time to hate; a time for war, and a time for peace.” These are traditional principles of balance that apply today also.

In traditional times, obesity was considered out of balance. Proverbs 11 describes this “A false balance is an abomination to the Lord, but a just weight is his delight.” This can also be understood as using a balance to weigh and depending on a just weight for accuracy. Second, Timothy teaches in verse 1 “For God gave us a spirit not of fear but power and love and self-control.” We are advised to practice self-control which is part of our spirits. Third John verse 1 tells us that good health and spirituality are linked. “Beloved, I pray that all may go well with you and that you may be in good health, as it goes well with your soul.” Self-control and maintaining a just weight are tied to our spirituality.

Spirituality is encouraged in the Bible as a way of achieving balance and a good life. First John 1 admonishes, “Do not love the world or the things in the world. If anyone loves the world, the love of the Father is not in him. All that is in the world—the desires of the flesh and the desires of the eyes and pride in possessions—is not from the Father but the world. And the world is passing away along with its desires, but whoever does the will of God abides forever.” In other words, being spiritual and avoiding the desires of the flesh, like over-eating, are helpful to us.

First Corinthians 6 tells us how important our bodies are “Or do you not know that your body is a temple of the Holy Spirit within you, whom you have from God? You are not your own.” In other words, living a healthy life in balance is a spiritual necessity since the Holy Spirit dwells within us.

The Bible also encourages exercise and hard work as in Matthew 11 “Come to me, all who labor and are heavily laden, and I will give you rest. Take my yoke upon you, and learn from me, for I am gentle and lowly in heart, and you will find rest for your souls. For my yoke is easy, and my burden is light.” We are told to find rest, replenishment, in spirituality after working hard.

We are also admonished that God will judge us as in Proverbs 16 “A just balance and scales are the Lord's; all the weights in the bag are his work.” Job 31 has a similar passage “Let me be weighed in a just balance, and let God know my integrity!” Just as God judges us, our bodies also tell us the truth about how well we live in balance. Chronic diseases, such as heart disease, type 2 diabetes and arthritis, afflict us when we are not in balance.

### 3. ISLAMIC FAITH

In the Quran, balance is mentioned several times. Transgression means the loss of balance. 40 Forgiver 28 “Truly God guides not one who transgresses and lies.” God encourages balance and guides those in balance. Ash-Shura, Chapter #42 tells us that “It is God who has sent down the Book (the Quran) in truth, and the balance (*i.e.* to act justly).” God tells us “Thus, we have made you a justly balanced community that you will be witnesses over the people” Surat Al-Baqarah 2:143. It is important for the community to be in balance. This is a crucial issue in traditional communities where only a certain number of people can be supported by the social structure. In order for people to survive, the community must be in balance.

“Every praiseworthy characteristic has two blameworthy poles. Generosity is the middle between miserliness and extravagance. Courage is the middle between cowardice and recklessness. Humanity has been commanded to avoid every such blameworthy trait” Lisan al-Arab 15/209. Balance in personality characteristics is as important as balance in health characteristics. Moderation is encouraged and helps people stay in balance. A man who fasted all day and prayed all night was told, “Do not do so. Fast and break your fast, pray in the night and sleep. Verily, your body has a right over you, your eyes have a right over you, and your wife has a right over you” Sahih Bukhari 4903. This shows the importance of fasting and praying to maintain balance. Fasting can help maintain the balance of the body. “You have a duty to your Lord, you have a duty to your body, and you have a duty to your family, so you should give each one its rights” Sahih Bukhari 1867. Spirituality and maintaining good health are important to living a balanced life [2].

### 4. HINDUISM

The Maitrayaniya Upanishads teach us “those who realize the Self enter into the peace that brings complete self-control and perfect patience. They see themselves in everyone and everyone in themselves.” The Self is Brahman (God), who lives inside each person’s heart. Therefore, spirituality and bodily health are intertwined.

Prajapati, the Lord of all creatures, divided himself into five pieces and entered into all living creatures. Prana is upward breath, inhaling and taking in energy. Apana is downward breath, exhaling and using energy. Vyana is the circulation of energy that maintains a balance between Prana and Apana. Samana is exertion and the digestion of nutrients to fuel exertion. Udana is the energy of the brain

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## **The Family and Balance**

**Abstract:** Balance in the family depends on having positive attitudes, good communication and the ability to make decisions together. Families must be able to adapt to challenges such as the end of life, serious diseases, depression, mental disorders, and poor health decisions such as obesity. Child abuse can tear families apart. More approaches to the treatment of adults who are child abusers are needed.

### **1. INTRODUCTION**

Childhood development, mental and physical health are influenced by the family [1]. It is important for the family to provide a supportive, positive and stable environment for the child to develop. This is a challenge for most families, given the economic and political changes that are occurring in the world today. Of course, the mental and physical well-being of the parents is supported by good family health as well.

The life balance model [2] can be modified to define family balance. Family balance is a satisfying pattern of daily activity that is healthful, meaningful and sustainable to a family within the life circumstances of the family. Everyday family activities should: be safe and enhance biological health; involve rewarding and self-affirming relationships; help family members feel engaged, challenged and competent; create a family identity. This model has been tested and validated in terms of individual life balance [2] and could be tested as a model of family balance.

Balance is important in family health and is defined as balancing time spent at work, together with the family, during social activities and taking care of oneself [1]. Families must prioritize the family and devote time together such as in the morning, evening, weekends and on vacation. This helps families have shared visions of future goals and supportive communication.

Awareness and reflection are mediators of family health [1]. Each member should be aware of the needs of other members and the problems created by the actions of others. Bad behavior such as lying and stealing should not be tolerated and not



excused. Positive reflection and supportive communication can help modify behavior and lead to improved family health. Rewarding good behavior and good performance reinforces this behavior.

The family needs to adjust, adapt and change as the family situation changes [1]. This includes changes in employment, births, deaths and other changes. Families have identities based on shared experiences, beliefs, values and preferences. This identity may change as the family matures together and shares new experiences.

Each family experiences trying times, such as loss of employment, chronic illness, or senility [1]. Families that adapt to these challenges have better family health. It is during trying times that the bad behavior of one member can damage the family. This bad behavior must be met with positive reflection and supportive communication.

Kindness, repentance and forgiveness are critical to individual and family health [3, 4]. Of course, family members love each other, but are they kind to each other? Kindness and love are very different qualities to some people. It is common for an abusive parent to tell the child, "I love you. But I have to teach you a lesson. I am doing this for your own good." Kindness means to be generous and considerate without expecting a reward. Repentance involves an apology, making changes to ensure the mistake does not happen again and making restitution to compensate for the damage done. Forgiveness means accepting repentance without retaliation.

## **2. CONSEQUENCES OF FAMILY LIFE**

Adults make sacrifices for their families [5]. Women, especially, find it hard to advance their careers while being mothers. With housing prices and the cost of living to increase, it is required for both partners in a marriage to work in order to buy a house and live as a family. On the other hand, working can make it more difficult to be a parent, especially for women. About 28% of working parents had to decrease work hours or take significant time off to take care of their families. About 15% of parents had to quit work to take care of their families. However, nearly 90% of parents who experienced career interruptions did not regret these experiences.

## **3. CARING FOR FAMILY MEMBERS AT THE END OF LIFE**

Caring for a mother, father or other family members at the end of life is very challenging [6]. As the cost of long-term health care for these patients becomes prohibitive for most families, a family member is usually assigned to care for the

dying family member. Frequently, the patient will display bad behavior such as abusive language and uncooperative behavior. It is important not to make excuses for this behavior. The family must support the person who has been assigned to provide health care. Sometimes, temporary nursing care is purchased to help during trying times. It is best for the family and the patient when the family remains a cohesive unit.

The most difficult decision for many families is physician-assisted death. Especially for families of patients suffering from Alzheimer's disease, the monthly assisted living cost is exorbitant and is not covered by health insurance. As discussed in the spirituality chapter, during traditional times, the Chumash Indians of California allowed these patients to decide when and where to end their lives. In this way, they died with dignity and were not a burden to their families. Physician-assisted death is not illegal in 10 states in the US [7]. Patients must be suffering from a terminal illness with no more than 6 months to live. This precludes patients suffering from Alzheimer's disease. So far, physician assisted death is used by several hundred patients yearly in the US.

Alzheimer's disease has become a major burden for many families since medicine can keep people alive long enough to develop the disease. Even after being diagnosed with Alzheimer's disease, it is common for patients to live another 7 years or more. The cause of Alzheimer's disease is not known. For many years, the dogma was that amyloid caused the disease. This dogma was supported by many publications. However, drugs that decrease brain amyloid plaques do not ameliorate Alzheimer's disease [8]. It is obvious that the disease is caused by other mechanisms, such as a leaky blood-brain barrier [9].

Cancer is another severe challenge for families. Families must not panic and remember that cancer is no longer a death sentence. Up to 70% or more cancer patients survive most cancers. Family members can become caregivers to cancer patients, including driving patients to doctor's appointments, chemotherapy and surgery visits, helping patients understand the disease and its treatments, helping patients with the side effects of chemotherapy, and more [10]. A critical therapy the family can provide is to cheer up the patient and help them avoid depression. The family should discuss "what if" scenarios with the patient so they are prepared for what might happen. The patient should also appoint one family member to help make do not resuscitate or other end-of-life decisions for the patient if necessary.

## Immunity and Balance

**Abstract:** The immune system depends on gut health and diet. Exercise, senescence and diseases also alter the homeostasis of the gut and other lymphoid tissues which affects the immune balance of the body. A healthy lifestyle is probably the most important therapy a patient can employ to maintain immune health.

**Keywords:** Alcohol, Autoimmunity, Diet, Exercise, Gut, Obesity, Senescence, Smoking.

### 1. INTRODUCTION

The body has many tissues that make up the immune system, skin, tonsils, adenoids, thymus, bronchus-associated lymphoid tissue, bone marrow, spleen, appendix and lymph nodes in various places. The immune system includes the Peyer's patches in the intestines, which are sites of maturation of many immune cells. Macrophages, T cells, B cells, M cells and dendritic cells in the Peyer's patches are critical to immune defenses against bacteria, viruses and fungi introduced into the gut.

Barriers such as the skin, GI tract, respiratory airways, nasopharynx, eyes and blood-brain barrier, are essential for keeping infectious organisms out of the body. The innate immune system prevents or limits infections by pathogens due to cellular immune recognition of danger-associated molecular patterns (DAMPs) produced on the plasma membranes of damaged cells [1]. Immune cells also recognize pathogen-associated molecular patterns (PAMPs) released by pathogenic bacteria and viruses. This means that recognition of DAMPs and PAMPs by immune cell pattern recognition receptors helps keep the body in balance and free of infections. Cells involved in the innate immune system include macrophages, mast cells, dendritic cells, natural killer cells and  $\gamma\delta$  T cells.

The adaptive immune system is activated once a pathogen enters the body [2]. B cells make antibodies that are part of the immunologic memory and are made for

specific non-self antigens. T cells secrete cytokines that help defeat invading pathogens. Stress is immunosuppressive, as has been discussed in the lifestyle chapter.

There is also a neuroimmune system that protects the brain from infections [3]. This involves T cells, B cells and the formation of antibodies and cytokines. The first line of defense of the brain is the blood-brain barrier that prevents most pathogens from entering the brain. In the brain, astrocytes, microglial cells, oligodendrocytes and mast cells protect neurons from infections and other damaging influences.

## **2. GUT HEALTH AND THE IMMUNE SYSTEM**

Peyer's patches in the ileum, jejunum and duodenum are where the immune system can be directly influenced by diet. Pathogenic organisms in the gut are processed by macrophages, dendritic cells and M cells in the Peyer's patches [4]. This leads to T cell, B cell and memory cell activation near the Peyer's patches and immune cell amplification in mesenteric lymph nodes. Macrophages, dendritic cells and M cells have processes that directly contact the gut contents.

The Vagus nerve innervates the guts and is responsible for an anti-inflammatory effect through the activation of nicotinic receptors [NACHR, 5]. Vagal nerve stimulation decreases the production of TNF, IL-1 $\beta$ , IL-6 and IL-18. Gut myenteric neuron stimulation results from Vagal stimulation, blocks the activation of inflammatory Th17 cells, and activates anti-inflammatory Treg cells. There is a feedback mechanism to the brain involving peripheral IL-1 receptors on Vagal nerves.

The intestinal mucosa is persistently challenged by food and introduced allergens. A balance between defense and tolerance must be maintained. When this balance tips toward defense, pathology can occur, such as inflammatory bowel disease or Celiac Disease induced gluten intolerance. Vagal tone may be important in re-establishing tolerance and stopping inflammation. One of the most effective ways to increase vagal nerve outflow from the brain is by exercise. Smoking introduces nicotine into the guts and appears to decrease the severity of ulcerative colitis in patients [5]. Nicotine interacts with NACHR on Th2 cells and on nicotinic neurons [5] in this regard. However, several immune cells express NACHR, including macrophages, B cells, T cells and dendritic cells [5].

Decreased Vagal tone is a critical issue in heart patients and makes the heart less efficient. As Vagal tone decreases, inflammatory cytokines such as C-reactive protein are released by immune cells, gut cells and other cells. This leads to

increased mortality in congestive heart failure [5].

### **3. DIET AND THE IMMUNE SYSTEM**

Many flavonoids and other phenolic compounds have been reported to enhance immunity throughout the body. A number of these flavonoids are not well absorbed in the gut. It is critical to remember that dendritic cells, macrophages and M cells in the Peyer's patches come into contact with these compounds in the gut, even if they are not absorbed into the blood. These cells alter and enhance the gut immune response that affects the entire body. These compounds alter the immune system without being absorbed into the blood.

Humans have eaten vegetables and fruits for the entire span of our existence. Our bodies have responded and adapted to diet derived compounds. It is not surprising that plant derived flavonoids have become essential to our health and our immune health.

Chocolate contains several flavonols, including epicatechin (Fig. 1) . Eating dark chocolate decreases blood pressure, increases flow mediated dilation and decreases insulin resistance [6]. Chocolate is also anti-inflammatory since it decreases adhesion molecule expression on leukocytes. Cocoa flavan-3-ols are cardioprotective since they decrease sE-selectin levels, a marker of leukocyte adhesion and endothelial function [6]. Epicatechin increases NO production, decreases blood glucose, insulin and insulin resistance [6]. Several genes involved in adipogenesis and inflammation are altered by epicatechin ingestion. It should be mentioned that a large portion of oral epicatechin is not absorbed in the intestines but is metabolized by gut microbes. These metabolites are absorbed into the blood and have pharmacological activities.

## The Endocannabinoid System and Balance

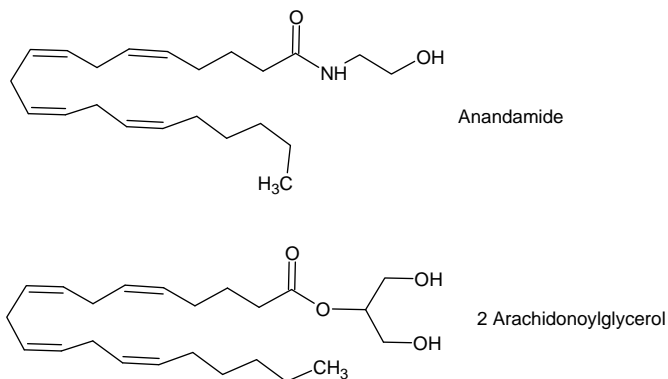
**Abstract:** The endocannabinoid system is a complex, redundant system that maintains the balance of normal health. It is a part of the eicosanoid system and interacts extensively with various eicosanoids and their receptors. Imbalance in the endocannabinoid/eicosanoid system leads to diseases that can be chronic and life-threatening, such as pain, diabetes, epilepsy and post-traumatic stress disorder. Plant-based medicines can be used to reestablish the necessary balance and effectively treat these disorders. However, it is always best to live in balance and allow the body to heal itself.

**Keywords:** Anxiety, Arthritis, Autism, Cancer, Cannabinoids, Chronic Ain, Chronic Fatigue Syndrome, Eicosanoids, Epilepsy, HIV/ADIS, Irritable Bowel Syndrome, Migraines, Multiple Sclerosis, Obesity, Pain, Post-traumatic Stress Disorder, Psoriasis, Traumatic Brain Injury, Type 2 Diabetes.

### 1. INTRODUCTION

The endocannabinoid system, endocannabinoidome, consists of endocannabinoids, the synthetic enzymes that make them, the enzymes that degrade them, and the receptors they interact with [1]. The endocannabinoids (Fig. 1) are N-arachidonoyl ethanolamine (anandamide) and 2-arachidonoylglycerol (2AG). Endocannabinoids are involved in homeostasis at the cellular and organ levels. Disruption of this balance is critical to several diseases. The endocannabinoidome is involved in cognition, fertility, pregnancy, fetal development, infant development, immune functions, appetite, pain, memory, mood and other functions.

Since the endocannabinoid system is critical to health, the body has several redundant pathways for the synthesis and degradation of endocannabinoids [1]. Receptor promiscuity is another hallmark of the system; in other words, an agonist for one specialized receptor, such as a prostaglandin receptor, may interact with another specialized receptor, such as an endocannabinoid receptor. This makes the system very complex and difficult to manipulate with agonists or antagonists.



**Fig. (1).** Endocannabinoids.

The receptors that endocannabinoids interact with include cannabinoid receptor 1 (CB1), cannabinoid receptor 2 (CB2) and several other receptors. CB1 and CB2 are G-protein coupled receptors. Most CB1 receptors in the brain are presynaptic, but some postsynaptic and astrocytic CB1 receptors have been reported [2]. CB1 presynaptic receptors inhibit the release of glutamate and  $\gamma$ -aminobutyric acid (GABA). Endocannabinoids also interact with transient receptor potential cation channels. CB1 is most abundant in the brain, but is also found in many other tissues [1]. CB1 receptor activation is involved in dysbiosis, an imbalance of gut bacteria that can be accompanied by increased intestinal permeability. CB2 is primarily found on immune cells but is found on microglia and other places as well. CB2 receptors are involved in the regulation of leakage across the blood-brain barrier [1].

The enzyme that makes anandamide is N-acylphosphatidylethanolamine specific phospholipase D like hydrolase (NAPEPLD). This enzyme makes other N-acylethanolamines as well [1]. Some of these are putative endocannabinoids. Anandamide is made upon demand in the postsynaptic terminal, is released into the synapse, where it acts on presynaptic CB1 receptors and is degraded. There is no vesicular storage of anandamide. Anandamide is an agonist for CB1, CB2, peroxisome proliferator-activated receptor  $\gamma$ , and an antagonist for Cav3.2 calcium channel, transient receptor potential cation channel vanilloid 1 (TRPV1), and TRP melastatin 8 (TRPM8). It is both an agonist and an antagonist for TRPV1 since long-term activation leads to inhibition.

Brain TRPV1 binding by endocannabinoids stimulates hunger, fear, anxiety, and memory [1]. The activation of brain peroxisome proliferator-activated receptor (PPAR)  $\alpha$  and  $\gamma$  by endocannabinoids is neuroprotective and anti-inflammatory.

The enzyme that degrades anandamide is fatty acid amide hydrolase (FAAH) which is a membrane-bound enzyme. This enzyme also degrades other N-acylethanolamines and fatty acid amides [1]. The enzyme works very rapidly to degrade anandamide and stop its actions.

The synthesis of monoacylglycerols, including 2AG, is catalyzed by diacylglycerol lipase  $\alpha$  and  $\beta$  [1]. This occurs on-demand in the postsynaptic terminal. There is no vesicular storage of 2AG. The release of 2AG into the synapse allows it to interact with presynaptic CB1 receptors. 2AG is a more effective agonist for CB1 than anandamide. 2AG is degraded rapidly by monoacylglycerol lipase, a membrane-associated enzyme. Other receptors that 2AG is an agonist for include TRPV1 and GABA<sub>A</sub>. 2AG and anandamide are also broken down by cyclooxygenase-2, which means that inhibition of cyclooxygenase-2, such as by nonsteroidal anti-inflammatory drugs increases endocannabinoids and decreases prostaglandins [2].

Several endogenous compounds interact with the endocannabinoid system. N-Acyl-dopamines, fatty acid primary amides, N-acyl-serotonins, N-acyl-taurines and N-acyl-amino acids all have their own receptors but can also interact with endocannabinoid receptors. This contributes to the complexity and redundancy of the endocannabinoid system.

## 2. OBESITY

Endocannabinoids are made by visceral fat and secreted into the blood [3]. They act on visceral fat cells as paracrine mediators to decrease adiponectin production and increase the production of inflammatory adipokines, including visfatin and tumor necrosis factor  $\alpha$ . These adipokines are involved in causing several diseases, as discussed in the lifestyle chapter. This demonstrates the importance of living in balance. Too much endocannabinoid synthesis in obesity produces a proinflammatory condition. The right amount of endocannabinoids is required for normal health.

## 3. PROSTAGLANDINS AND OTHER EICOSANOIDS

Arachidonic acid is the starting material for endocannabinoids, isoprostanes, prostaglandins, leukotrienes, thromboxanes, lipoxins and other compounds (Fig. 2 - 5). All of these eicosanoids exist in a balance. When the body needs prostaglandins, the synthesis of other eicosanoids may decrease. When the demand for endocannabinoids increases in an organ, the synthesis of other eicosanoids may decrease temporarily. Some eicosanoids are kept separate from



## The Antioxidant System and Balance

**Abstract:** The body is protected by glutathione, the most important antioxidant. Glutathione protects the body from oxidative stress, hydrogen peroxide toxicity and lipid peroxidation. Patients seek dietary antioxidants to help with their health. Lifestyle changes such as daily exercise and getting rid of excess weight help maintain glutathione and health.

**Keywords:** Antioxidants, Catalase, Gamma-glutamyl transferase, – Glutaredoxin, Glutathione peroxidase, Glutathione, Hydrogen peroxide, Isoprostane, Peroxiredoxin, Pyroglutamate, Vitamin E.

### 1. INTRODUCTION

The body depends on antioxidants for protection against reactive oxygen species and other reactive species that derive from the fact that humans breathe air. Air is processed in the mitochondrial oxidative phosphorylation system to make ATP. A side product of this respiratory system is the generation of reactive oxygen species such as superoxide radical anion that interacts with superoxide dismutase or manganese superoxide dismutase to form hydrogen peroxide. Oxygen radicals produced by this system are short-lived and do not usually cross mitochondrial and other membranes. It has been estimated that 0.1-2% of the oxygen used by mitochondria makes a superoxide radical anion [1]. Hydrogen peroxide crosses membranes due to channels called peroxiporins and is a powerful oxidant that within minutes damages DNA and other macromolecules [2]. The body detoxifies hydrogen peroxide through the actions of peroxiredoxins, glutathione peroxidase and catalase.

### 2. HYDROGEN PEROXIDE SIGNALING

Hydrogen peroxide transmits signals from one organelle to another since it crosses membranes at peroxiporin pores. It readily penetrates into the nucleus, damages DNA and activates poly(ADP-ribose) polymerase [3, 4]. Poly(ADP-ribose) polymerase upregulates the transcriptional activity of nuclear factor erythroid 2 related factors 2 (Nrf2) and enhances the interaction between antioxidant response elements (ARE), Nrf2 and MafG [5]. Nrf2 is a transcription factor that is involved in the regulation of redox homeostasis, such as during

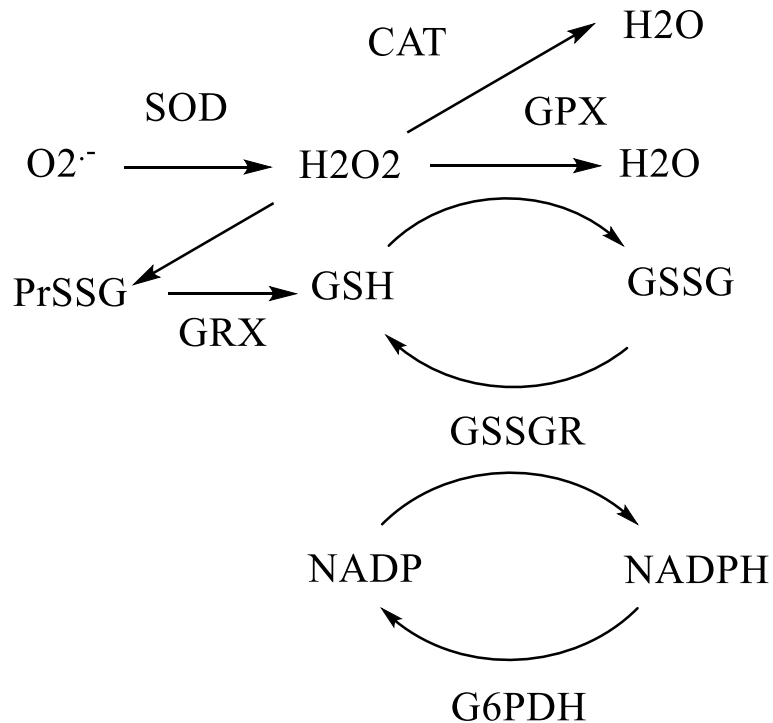
oxidative stress. It is normally found in the cytosol but is translocated into the nucleus during oxidative stress, where it is stabilized by heterodimerization with small Maf proteins, such as MafG. Poly(ADP-ribose) polymerase binds to ARE and NafG, which enhances the ability of Nrf2 to bind to ARE and MafG. This increases the transcription of Nrf2 target genes. These genes include glutathione transferase, NADPH dehydrogenase (quinone 1), glutamate-cysteine ligase, sulfiredoxin 1, thioredoxin reductase 1, heme oxygenase 1, UDP glucuronosyltransferase, and multidrug resistance-associated proteins.

P53 is stabilized by cytosolic NADPH dehydrogenase (quinone 1) [6], and is involved in the regulation of DNA repair genes. The progression of apoptosis is controlled by P53. This is involved in hydrogen peroxide induction of a number of apoptosis-inducing and inhibiting proteins [7].

Hydrogen peroxide also oxidizes sulfur, such as in cysteine to sulfenic (SOH), sulfinic (SO<sub>2</sub>H), and sulfonic (SO<sub>3</sub>H) acids [8]. It promotes the formation of disulfides between proteins and glutathione. Nrf2 is normally deactivated following ubiquitination by Kelch-like ECH-associated protein 1 (KEAP1). This leads to proteasomal degradation. Hydrogen peroxide oxidizes Cys151, Cys171, Cys273, Cys288 of KEAP1, which decreases its activity and inhibits its ability to deactivate Nrf2. Several other protein cysteines are oxidized by hydrogen peroxide leading to changes in activity, including forkhead box O3 transcription factor, NFκB subunits and tumor suppressor phosphatase (PTEN).

### 3. CATALASE

Catalase is a heme enzyme found in peroxisomes (Fig. 1) that can change millions of molecules of hydrogen peroxide into water and oxygen every second [9]. Catalase also uses hydrogen peroxide to oxidize ethanol, formaldehyde, formic acid, phenols, acetaldehyde and other compounds. NADPH is tightly bound to catalase and is involved in hydride transfer that prevents the deactivation of catalase and accumulation of compound II, the inactive form of catalase [10]. Humans born with little catalase activity, acatalasemia usually have normal health.



**Fig. (1).** The glutathione antioxidant system. Glutathione (GSH) and glutathione disulfide (GSSG) interact with hydrogen peroxide formed by superoxide dismutase (SOD). Glutathione peroxidase (GPX) catalyzes the detoxification of hydrogen peroxide. Glutathione disulfide reductase (GSSGR) maintains the glutathione redox state at the expense of NADPH. NADP is reduced by glucose-6-phosphate dehydrogenase. Catalase also detoxifies hydrogen peroxide. Hydrogen peroxide oxidizes protein figuresulphydryls forming glutathione-protein mixed disulfides (PRSSG).

Peroxisomes are found in every cell in the body and are involved in hydrogen peroxide detoxification, very long-chain fatty acid catabolism, branched-chain fatty acid catabolism, production of plasmalogens and other functions [8]. Plasmalogens are ether phospholipids that are important in the membranes of heart and brain cells, especially myelin [11].

#### 4. GLUTATHIONE

Glutathione is a tripeptide,  $\gamma$ -glutamyl-cysteinyl glycine, and is the most important antioxidant in the body. It is synthesized in the cytoplasm of every cell due to the actions of glutamate-cysteine ligase and glutathione synthetase. Glutamate cysteine ligase makes  $\gamma$ -glutamylcysteine at the expense of ATP. Glutathione synthetase adds glycine to this at the expense of ATP. Glutamate cysteine ligase is the rate-limiting enzyme in glutathione synthesis and is

## The Energy Balance of the Body

**Abstract:** The body depends on NAD to indicate/sense the energy levels in the body. When energy is normal, sirtuins respond to fluctuations in energy demands and regulate gene transcription. When the body is under an oxidative challenge, poly(ADP-ribose) polymerase responds to DNA strand breaks and increases the activities of DNA repair enzymes. NAD and ATP are closely linked in the cell since they are both high-energy adenine nucleotides and are mutually required for their own synthesis.

**Keywords:** Exercise, Poly(ADP-ribose) Polymerase, NAD, NADPH Oxidase, NADH Oxidase, Nicotinamide, Sirtuin.

### 1. INTRODUCTION

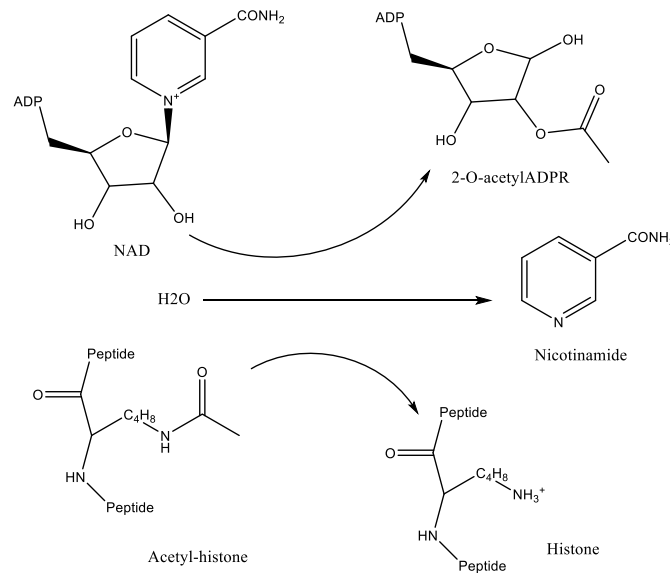
There is an energy balance in the body that depends on ATP, cAMP, NADPH, NADP, NADH and other factors. These factors protect DNA, mitochondria, proteins and lipids that are vital for cell repair and survival. They are also involved in respiration and the transportation of nutrients into cells.

NAD is an abundant molecule that exists in cells in concentrations of about 0.1 to 0.6  $\mu\text{mole/g}$  of tissue [1]. It is a dinucleotide of nicotinamide and adenine linked by two high energy phosphate bonds. The beta anomer of NAD is the natural form and contains D-ribose sugars. NAD is the switch that senses energy deficits or excesses and adjusts enzyme activities and genetic expression of enzymes to reestablish energy balance [2, 3]. Two enzymes are critical to this switching process, poly(ADP-ribose) polymerase and sirtuins.

It should be mentioned that quantitating NADPH and NADH requires the proper methodology [1]. These compounds oxidize readily in biological extracts due to the presence of iron. The addition of cyanide during extraction allows cyanide to chelate iron, preventing oxidation. Cyanide also derivatizes NAD and NADP, making them fluorescent for better HPLC detection.

## 2. SIRTUINS

Sirtuins are the energy switches in normal cellular physiology. They respond to NAD changes and alter the activities of histones and other proteins. Sirtuins deacetylate the lysines of various enzymes, which alters their activities [4]. The mechanism of this deacetylation is shown in Fig. (1). However, sirtuins can also function as ADP-ribosyl transferases, which will be discussed later. Sirtuins contain a Rossman fold, a zinc-binding site and a NAD binding site [4]. The NAD binding of sirtuins leads to ADP-ribose binding to enzymes that cause lysine deacetylation and the formation of 2-O-acetyl ADP ribose (Fig. 1). In a mechanism similar to deacetylation, sirtuins can deacylate enzymes by removing malonate, succinate, glutarate and other compounds. There are 7 human sirtuins, each with different activities and subcellular locations [5, 6] as shown in Table 1. Each of these enzymes can be inhibited by nicotinamide, a product of enzymatic action, in a feedback mechanism. This feedback mechanism involves the fact that the enzymes can function in reverse and use nicotinamide to make NAD [4].



**Fig. (1).** Mechanism of deacetylation by sirtuins.

It should be mentioned that there are many histone deacetylase enzymes, not just sirtuins. These enzymes regulate epigenetic processes. Sirtuins bind NAD, which makes them different from other histone deacetylases. Several anticancer drugs are available that inhibit histone deacetylases: vorinostat, Panobinostat, belinostat and chidamide.

**Table 1.** Sirtuin subcellular locations, activities and targets. Hif is hypoxia inducible factor. MYC is a family of regulatory genes and proto-oncogenes. FOXO are the forkhead family of transcription factors. EIF are the eukaryotic initiation factors. P53 is a tumor suppressor protein. G6PD is glucose-6-phosphate dehydrogenase. SOD is superoxide dismutase. PDMC is pyruvate dehydrogenase multienzyme complex. IDH is isocitrate dehydrogenase. GOT is the gene that encodes aspartate aminotransferase. GDH is glutamate dehydrogenase. PDH is pyruvate dehydrogenase. CPS is carbamoyl phosphate synthetase. GSK is glycogen synthase kinase. LEF is lymphoid enhancer factor. PPAR- $\alpha$  is peroxisome proliferator activated receptor. DGAT1 is diglyceride acyltransferase. UPR is unfolded protein response. NRF is nuclear respiratory factor.

	Subcellular Location	Enzymatic Activity	Histone Target	Nonhistone Target
Sirtuin-1	Nucleus, cytoplasm	Deacetylation	H3K9Ac, H1K26Ac H4K16Ac	Hif1 $\alpha$ , Hif2 $\alpha$ , MYC, P53, FOXO
Sirtuin-2	Nucleus, cytoplasm	Deacetylation	H3K56Ac, H4K16Ac	Tubulin, FOXO3a, EIF5A, P53, G6PD, MYC, GSK3 $\beta$
Sirtuin-3	Mitochondria	Deacetylation	H3K56Ac, H4K14Ac	SOD2, PDMC1a, IDH2, GOT2, FOXO3a
Sirtuin-4	Mitochondria	ADP-ribosylation	Unknown	GDH, PDH
Sirtuin-5	Mitochondria	Malonyl, Succinyl, Glutaryl deacylation	Unknown	CPS1
Sirtuin-6	Nucleus	Deacetylation, ADP- ribosylation, long chain fatty acid deacylation	H3K9Ac, H3K56 Ac	LEF1, PPAR- $\alpha$ , DGAT1
Sirtuin-7	Nucleus	Deacetylation	H3K18Ac	Hif1 $\alpha$ , Hif2 $\alpha$ , UPR, NRF

### 3. OBESITY

Sirtuins affect the activities of many genes. For instance, obesity alters the expressions of SIRT1, SIRT2, SIRT3 and SIRT6 [7]. This alters the expressions of their target genes, PPAR- $\alpha$ , progastricsin PGC1- $\alpha$ , NRF1, DGAT1, PPAR- $\gamma$  and FOXO3a. This shifts the physiology of obese patients to an inflammatory status.

Decreased sirtuin-1 activity in obesity increases the activities of PPAR- $\gamma$ , PGC1- $\alpha$  and FOXO3a. Both PPAR- $\alpha$  and PPAR- $\gamma$  have anti-inflammatory activities [8], indicating that their upregulation is a compensatory mechanism against other inflammatory activities. PGC1- $\alpha$  is inflammatory in the stomach and small intestine [9] and also increases the number of mitochondria in cells [7]. Mitochondria produce reactive oxygen species that can damage cells, as will be discussed later. FOXO3a promotes and maintains inflammatory leukocyte

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**James David Adams**

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