Session 1 Primary Care Conference Chico Hot Springs
What is a “Normal” Human Diet?
What is wrong with the Usual American Diet?
Hypertension, Vascular Disease, Pregnancy

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References

In a separate PDF document called References.pdf is a list of references relevant to the subject being discussed. Some of the references have a web site listed so those references can be found on the web. If the identifier called DOI is in the reference, copy and paste it into Google search and it will take you to the article. References without web addresses are obtainable through Pub Med or through a medical library or sometimes by putting the reference into a search engine such as Google. Some of the references are books or news articles, but most are journal articles. The numbers in brackets are the references, such as [2, 3, 9].

Introduction

I am a Family Physician. I practiced full spectrum family medicine in Libby from 1977 to 2021. I was fortunate to be able to learn the long view of medical care. Some of the patients I saw in the first few years of practice, I continued to see throughout my career. I saw the evolution of the metabolic syndrome. I experienced how difficult it was to treat the wide variety of symptoms and illnesses that many times led to disability and a big downturn in patients’ lives. I became frustrated that health care was not focused on prevention, but only on treatment. What corporate health care calls prevention is often money-making early diagnosis. I was very upset that there was no significant public messaging about true prevention of so many common, serious, chronic diseases. It is obvious that the health care industry is putting profit far above prevention. Health care along with the food industry goes to great lengths to suppress what science has learned about preventing chronic disease.

I have had an interest in nutrition science since my college days. Being busy with family, my own busy practice of medicine and sports, I did not ever take time to dig into this important issue until I retired in February of 2021. Since then, I have read hundreds of articles and read many books on the subject. I was surprised to find that there is a huge amount of scientific information on this subject that spans many chronic illnesses. Science has uncovered what a healthy diet is and why Americans have so much chronic disease. I have been teaching a nutrition science class as part of community education at the Lincoln County Campus of Flathead Valley Community College the last 3 winters starting in February of 2023. I taught a nutrition class for chemotherapy patients. I also taught this course to the NW Community Health Center physicians, NPs, PAs, and their staff in Libby.

Putting it altogether, we, as health care providers, have been misled. We are supposed to believe that if only the patients will comply with taking their medications and change their lifestyles, they will be healthy. Our patients have become addicted to harmful foods & drinks

to the point that most of their calories come from these harmful foods. They can't afford their medications. They, along with us, have an incomplete or inaccurate understanding of what a "normal" human diet is and why the processed food diet is so harmful.

The food industries and big pharma want you to put the blame for your patient's misery on the patient's lifestyle choices. The truth is the blame is on the food industry for concocting and promoting addictive ultra-processed "food & drink" [1], and for the health care industry's great moral failure of not promoting and investigating true prevention in favor of profit [2, 3, 9].

Ultra-processed Foods & Drinks (UPF) *are confections* (things mixed together) *of ingredients extracted from whole foods usually combined with sophisticated use of additives* (experts estimate 10,000 different types of additives are approved by the FDA) *to make them edible, palatable, and **most importantly habit forming**.* (See the PDF document: Nova Classification of Foods.pdf.)

The goal of this class is to present what nutrition science has learned about prevention and treatment of common chronic diseases. I want you to be able to push aside all the noise about diet and disease we get bombarded with. I want you to open your mind to a **new way of thinking about chronic diseases**. Our foundation of nutritional knowledge will be based on scientific research dating back to the early 1900s up to the huge number of studies done in the last 15-20 years. This course casts aside studies funded by the food industry and/or big pharma because of their inherent bias in funding studies that produce misleading information that hide the truth about nutrition science and chronic disease. My hope is that you will come to blame the food industries and the major health care organizations for the harm they are causing your patients. I hope you will tell your patients it is not their fault they are hooked on UPF. They need our help, understanding, and education. Most of them either feel guilty about their problems or accept them as a normal part of life. What they need is the truth.

Another reason to learn the truth about common chronic diseases is that it will help with burnout feelings that most of us health care workers have experienced. Patients become disgruntled for many reasons: sitting in the waiting room too long, cost, debt, can't get into see a specialist for 6 months and lifestyle blaming. I think many patients sense the hypocrisy of a health care system that puts profit above their health. Most pertinent to what these lessons are about is our own participation in misleading our patients about the best ways to prevent and treat common diseases. By learning and acknowledging what science is telling us and conveying that to our patients, we gain respect and improve our professional relationship with our patients. We gain confidence that what we advise patients is scientifically sound and will help them prevent and treat common chronic diseases. It will help us take control of our professional lives and improve our job satisfaction. One thing I have taught medical students for years is that patients know a lot more about themselves than we realize. Our job is to help them understand themselves even better.

The plan is for 2 consecutive sessions. Prior to these sessions you will read the material sent to you and answer questions about the material. During each session we will review some of the questions for that session and any other questions you have. Then you will break into small groups and will be given a patient scenario and a series of tasks or questions about the patient. During the last part of each of the two session we will discuss your findings and recommendations. I think this will be fun and eye opening and give you a different perspective of chronic diseases.

What are the elements of a "normal" healthy human diet?

Science is making progress on uncovering what ancient humans ate (think twelve to twenty-five thousand years ago). Older evidence focused on the markings on animal bones as evidence that supported widespread eating of wild animals. Newer archeological investigations of sites dating back as much as 23,000 years ago [4] show evidence of early attempts to cultivate wild oats, barely and emmer (ancient form of wheat). More recently, newer techniques with amino acid analysis, DNA sequencing, and isotope studies, show that our ancient ancestors 15,000 years ago ate plenty of plant food [5]. By about 12,000 years ago, more human cultures were incorporating both domestication and eating of animals as well as cultivating plants for food. Simply stated it is likely humans have been omnivorous for thousands of generations. Scientific evidence now points out that plants as a source of food were more important than originally thought.

Jumping up to the early and middle 1900s, doctors and scientists became fixed on a new human plague. People in parts of the world that were modernizing were dying of heart attacks. Doctors and scientists became very focused on why more people were getting serious coronary disease.

In Papua New Guinea (large island country in Oceania north of Australia) primitive tribes in the Western Highlands were just beginning to change culturally in the 1960s and 70s [6-8]. Physicians there (mostly Australian) noticed a nearly complete lack of hypertension, diabetes or the typical atherosclerotic diseases of heart attacks, strokes, and vascular claudication in these tribespeople. Scientists in New Guinea and Australia did extensive studies on several hundred of these folks. What they found was that nearly all their caloric intake was from very natural foods that were not significantly processed. Further about 90% of their calories came from a wide variety of sweet potatoes. They did have hogs and chickens, but they were only eaten on special occasions. When they averaged out the caloric intake of meat, it was not a significant part of their diet.

Low rates of atherosclerosis were also found in the Bantu cultures of Africa in the 1950s [10-11]. A mine physician noted the lack of atherosclerotic disease in the Bantu but not the white miners. A prison study of miners compared western white workers with Bantu natives and found that when diets were reversed in prison that their lipid blood tests changed depending on the diet and was unrelated to their race. The white miners ate the more western diets and the Bantu mostly corn, lentils and stone-ground breads. Many other cultures have been studied as well and essentially show that cultures that eat predominantly natural plant food have extremely low rates of atherosclerosis and diabetes. No studies of cultures that eat predominately ultra-processed foods or primarily meat and dairy diets have shown low rates of these chronic illnesses. In fact, they show the opposite: the more UPF people ate, the higher their chances of getting one or more of these chronic diseases. From an epidemiological standpoint eating lots of natural minimally processed plant foods seems to prevent common chronic diseases. This includes common cancers such as colon, breast and prostate cancers.

In California a remarkable human study was done in the late 1970s [12-14]. A self-made research and development scientist, Nathan Pritikin, who patented many inventions and owned factories producing products based on his discoveries, also had a life-long interest in health care. He himself had developed coronary disease with reduced exercise tolerance, weight gain, elevated lipids, and an abnormal treadmill. He chose not to have a heart catheterization. His health science research suggested a diet mostly based on whole grains, vegetables and whole fruit with only small amounts of lean meats and low-fat dairy, likely would improve his heart disease. He switched his own diet, and over a few months he was feeling much better. The next year his labs and treadmill showed remarkable improvement.

He loved problem solving and always followed through with trying to prove he was correct in his reading of the science. He was able to convince the Chief Medical Officer at the Longview California VA Medical Center that his diet could help veterans crippled by coronary disease. Pritikin and the VA identified 12 patients with heart disease for the study. Two patients dropped out and one other tried to do the program at his own home. Pritikin was allowed to have a day center near the VA hospital where the 9 remaining veterans agreed to come every day for two months, only eat the food prepared at the day center, and take 3 walks a day. Pritikin's son was available these two months between taking his college classes. On the weekdays his son ran the center and documented the data. Pritikin hired a cook during the week and Pritikin and his wife took on these duties on the weekends. All 9 of these VA patients finished the two months. All of these veterans had in common being in one of the big wars. They suffered from chest pain, shortness of breath, and/or claudication. All had very poor exercise tolerance (Class 3 and 4 cardiac classification) and could not do sustained walks of more than 1 block or less without having to stop and/or take nitroglycerin. Some had arthritis, diabetes and/or hypertension as well. None were candidates for coronary bypass surgery.

There was much joking and griping about the food the first two weeks, but the 9 vets stuck with it. They enjoyed the comradery and were very interested in what Pritikin had to say and were encouraged by him. Within 2-3 weeks the veterans began noticing they could walk a little further and faster and the need for nitroglycerin and other meds was going down. Their own physicians at the VA were pleased at their progress and they supervised the reduction of their patients' medication. By 5-6 weeks it was clear that all 9 were significantly improving and Pritikin was astounded how well this simple diet that shunned processed foods was working. Blood tests were repeated at the end of the two months and were remarkably better. The patients' walking speed and distances all improved and they were feeling more energy and taking a lot less medications.

Doctors at Loma Linda University in California published the results. Pritikin later founded the Longevity Center that still exists today. Many thousands of patients have benefited from his institute as well his diet and exercise program that he published. He even was investigated by the TV program 60 minutes. They came to reveal a charlatan and discovered after interviewing many patients that his results were not a sham, but genuine. They even did a follow-up 60 minutes a couple of years later and interviewed some of the same patients. The Pritikin program became so famous that the major health care organizations and food industries disparaged him and continue to do so to this day. Many studies confirm the benefit of a mostly plant-based diet. Over the last 24 years we have learned why this type of diet is effective. If you look up Nathan Pritikin on Wikipedia, you can see how he is being discredited to this day 40 years after his death. Many other studies of similar diets have continued to show similar positive results [15-16], yet the major medical associations continue to downplay and ignore them.

Science over the last 30 or more years tells us that the traditional nutritional nomenclature is outdated. We need to learn 21st Century Nutritional Nomenclature.

Studies done in the last 15 years or so have cast aside the concepts promoted by traditional nutritionists and food scientists of looking individually at calories, carbs, fats, and protein.

1. Traditional nutrition emphasized caloric needs, but science tells us that we have a built-in mechanism for counting calories that is complex but amazingly accurate [131-132]. This mechanism often gets overridden by UPF causing gradual weight gain. Counting calories has been a failed weapon in our patients' battles with UPF for many years.
2. Carbs (which encompass simple sugars, starches, and fiber) is a very misused term, and should be replaced with the more accurate terms: Simple sugars (mono, di, or trisaccharides such as glucose, fructose, sucrose, lactose, maltose and raffinose). Starches (polysaccharides with often hundreds to thousands of connected monosaccharides) can be refined or processed such as white flour and corn starch. Starches can also be part of intact whole plant food such as in corn on the cob, whole wheat bread and pasta, rolled oats, beans, brown rice and nearly all other whole plant foods in various amounts and proportions. Fiber can be processed fiber from plants so that it is no longer part of a plant cell such as in Benefiber, Metamucil and Native Fiber. Healthy fiber is part of whole plant food items residing in the outer wall of plant cells such as in whole wheat bread or pasta, rolled oats, barley, beans, brown rice and essentially all whole plant foods.
3. Fats consist of animal fat that is naturally high in unsaturated fat such as in marbled meats, processed meats, eggs, milk chocolate, cheeses and other dairy products. Then there is processed plant oils. These include the healthiest plant oils that are high in monosaturated oils such as olive, canola, peanut and safflower oils, and the least healthy plant-based fats with significant amounts of saturated fats of coconut and palm oil.
4. The word "protein" is commonly misused so much that I think it has lost its meaning: For example: "I am going to grab a couple of protein bars for lunch" or "my body just needs more protein". All natural foods contain varying amounts of protein. Even raw honey has trace amounts of protein. Many adult Americans likely get too much protein. Studies of tribal peoples of New Guinea and Bantu of south-central Africa populations in the 1950-60s showed healthy adults did very well on diets with 5-10% of their calories as protein.

> High protein diets have been implicated in the development of osteoporosis. Native Inuit had high protein diets before 1960 and had very high rates of osteoporosis [133-135].

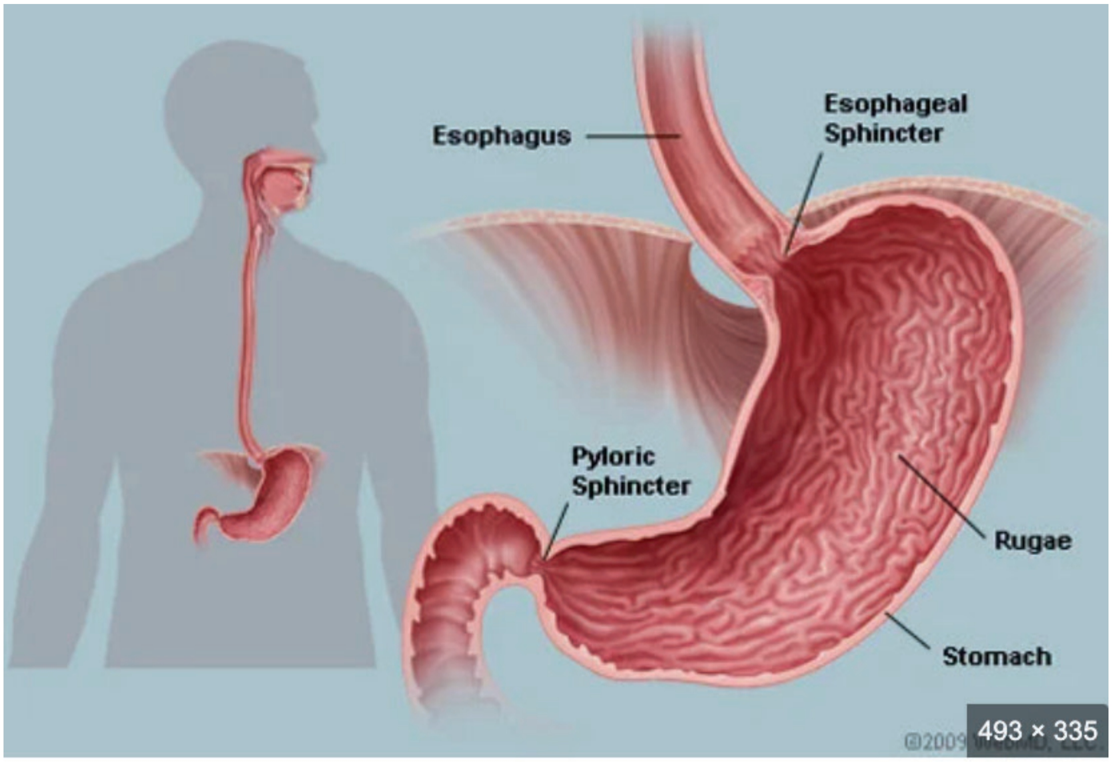
Diets focused on one or more of the old of categories of calories, carbs, fats and protein categories did not show significant prevention or treatment of common chronic diseases (vascular diseases of the heart, brain, kidneys, and legs, diabetes especially type 2, hypertension, obesity, dementias, depression, ADHD, arthritis and other autoimmune diseases, common cancers such as colon, breast, prostate and others). Unbiased studies now focus on why whole plant food is healthy, and on what is now called ultra-processed food & drink (UPF) and why it is harming so many people young and old.

Nutrition labels are not helpful. They break down the food in an unhelpful but historically traditional way. They list ingredients (but not all), many of which we have no accurate idea of what they mean. What we really want to know is how healthy the food is or how harmful it is, and is it palatable? Much to the delight of the food industry, it seems the only criteria for most foods we eat or recipes we like is how it tastes. We can evaluate the taste of a food, but we cannot evaluate healthiness or harmfulness of a food. The harm and healthiness are where all the confused noise about food comes in. The food industry prefers to focus on taste and has spent many decades perfecting new products that have become irresistible. The food industries participate at many levels along with Big Pharma in keeping us confused and focused on the old traditional model of "Calories, Carbs, Fats, and Protein". The new way of analyzing food is whether its ultra-processed or not. This is a bit of an oversimplification, but ultra-processed foods & drinks are harmful and real minimally processed whole plant food is healthy. (See Nova Classification of Foods.pdf for more details about meat and dairy products. Also, meat will be discussed more in Session 2.)

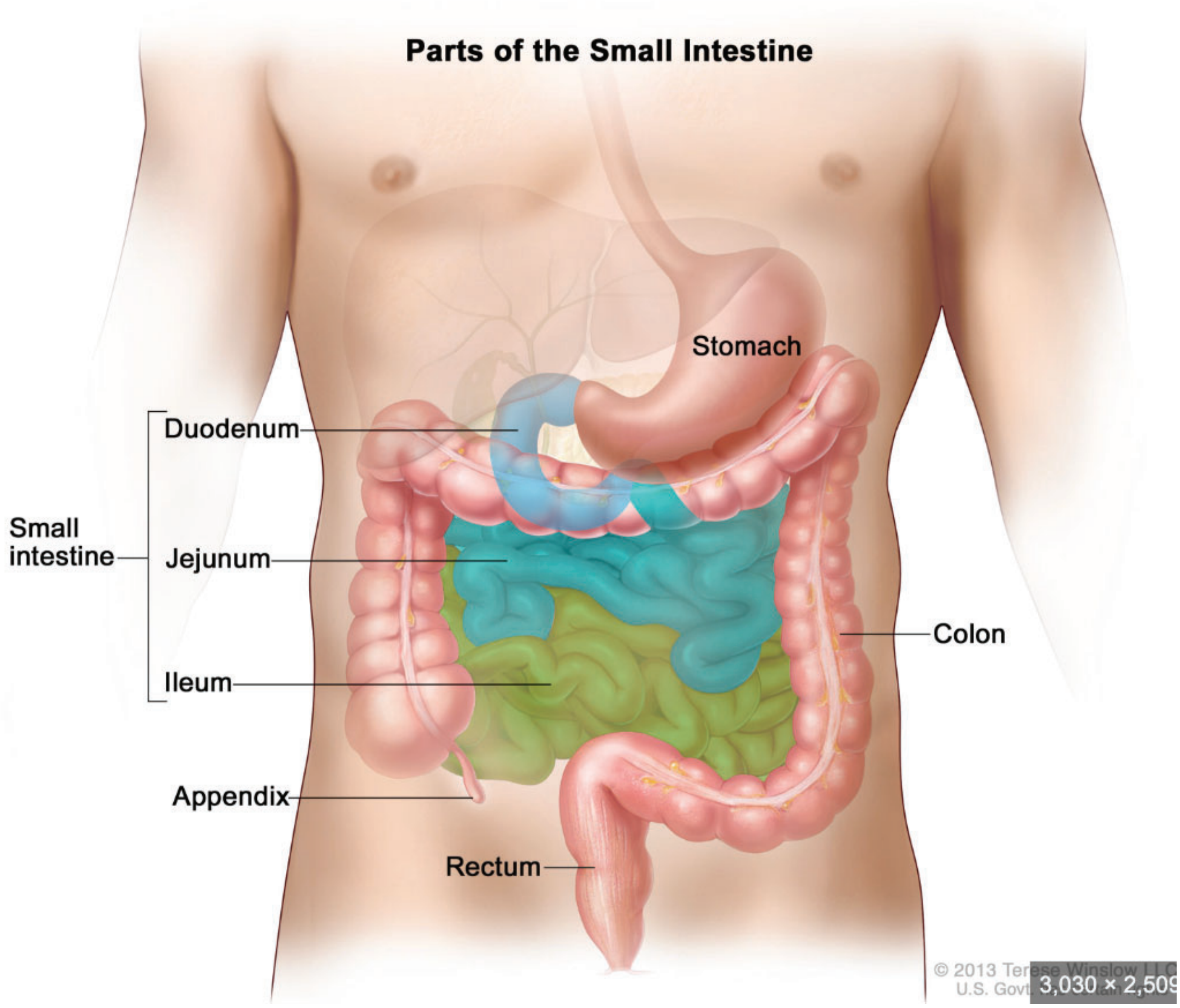
Overview of Digestion ***The illustration below is assuming a healthy young adult who does not have Insulin Resistance (also called Metabolic Syndrome or any of the diseases associated with it)***

Digestion in a healthy young adult begins before their first bite. Your brain knows you are going to eat. It senses this through your hearing, vision, sense of smell and so on. As you begin to eat, many hormonal and physiological changes occur. One of the many is insulin. This hormone begins to be released by the pancreas even before you absorb food or drink. Another change is in your brain. Through the autonomic nervous system, your brain tells your heart to pump a little more blood and tells the blood vessels in your digestive system to dilate. This is your brain telling your digesting system "It's time to get to work".

Chewing your food is the most potent stimulus of saliva production. It mixes with the food and begins some digestion of starch (such as in potatoes, whole grains, rice and beans). Equally important, saliva protects and heals the esophagus from being irritated by the stomach acid. Of course, if one chooses to drink or swallow minimally chewed food, then the esophagus has less protection and less healing of any sore spots.



The stomach has a variety of important functions. It continues the digestion of food by mixing it with potent acid as well as some digestive enzymes. The stomach, like the rest of the intestines, repeatedly squeezes the food back and forth to ensure good mixing. It communicates constantly with your brain giving it information about what you are eating and how much, and the brain sends back messages. The brain determines fullness based on many factors such as how full the stomach is, what foods you are eating, and whether the young adult needs more. The stomach gets signals as to how fast it should let the food pass into the small intestine for more complete digestion. In healthy folks who eat a large meal but do not need the calories right away, the stomach will meter out the food over many hours. If the person is behind on calories, the stomach will release the food much faster. While this is going on, the brain tells the arteries and veins of the intestines to open even more to provide more oxygen and nourishment so it can carry out the breakdown and absorption of the food being eaten.



Just beyond the distal end of the stomach is the pyloric sphincter that opens intermittently to meter out some of the partially digested food. Next is the beginning of the small intestine. The first part is a short segment of small intestine called the duodenum. At this upper part of the small intestine is the opening of the common duct that carries two types of fluids. The first is the bile from the liver that digests fats. The second type of fluid from the pancreas is loaded with the enzymes that further breakdown proteins, fats and oils, starches, and sugars. These enzymes continue the breakdown of the food as the small intestine moves the food back and forth, mixing it well with the cells that line the intestine. While moving its contents back and forth, it also moves the fluid along down the inside of the small intestine. Except for fiber, the 20-foot-long small intestine absorbs 90-95% of all the partially digested food coming from the stomach. Before the small intestine can absorb the food, it must break it down into simple sugars, fatty acids, glycerides, and amino acids.

The oils and fats are broken down into fatty acids and glycerides that enter the cells of the small intestine and form into protein coated chylomicrons which enter the lacteals (lymph capillaries).

These are passed directly into the circulation via the thoracic duct which empties into the left subclavian vein near the left side of your lower neck and upper chest. If you have your blood drawn 2 hours after eating pizza and let the blood sit in the test tube, a white layer will form. This white layer is composed of millions of chylomicrons (digested fats and oils converted into tiny packets of triglycerides and other substances)

The sugar molecules such as glucose, lactose and fructose, and amino acids made from the breakdown of starches, simple sugars and proteins enter the hepatic portal vein from the lining of the small intestine. Other drugs or food additives and vitamins also go into the hepatic portal vein and are processed in the liver.

The last part of the small intestine (called the ileum) empties into the right side of the large intestine called the cecum. The appendix is attached there.

Traditionally, for the last 50 years it has been taught that the colon absorbs water and minerals, gets rid of ruffage, and lets us know when it is time to sit on the toilet to empty the its contents. 21st Century Nutrition teaches us that the colon does so much more than this. It is one of the missing links between Insulin Resistance (the metabolic syndrome) and what we eat.

Insulin resistance was discovered in 1934 by H P Himsworth [18-20] who was a physician and researcher at the University of London. He is credited with the discovery of type 2 diabetes. It was not until 52 years later that the metabolic syndrome, which is triggered by insulin resistance, was presented by the endocrinologist and researcher at Stanford University, Gerald M Reaven MD. He gave the Banting Lecture at the American Diabetes Association (ADA) meeting in 1988. The ADA in 1997 finally came up with the classification of diabetes as type 1 and type 2, 61 years after type 2 was discovered.

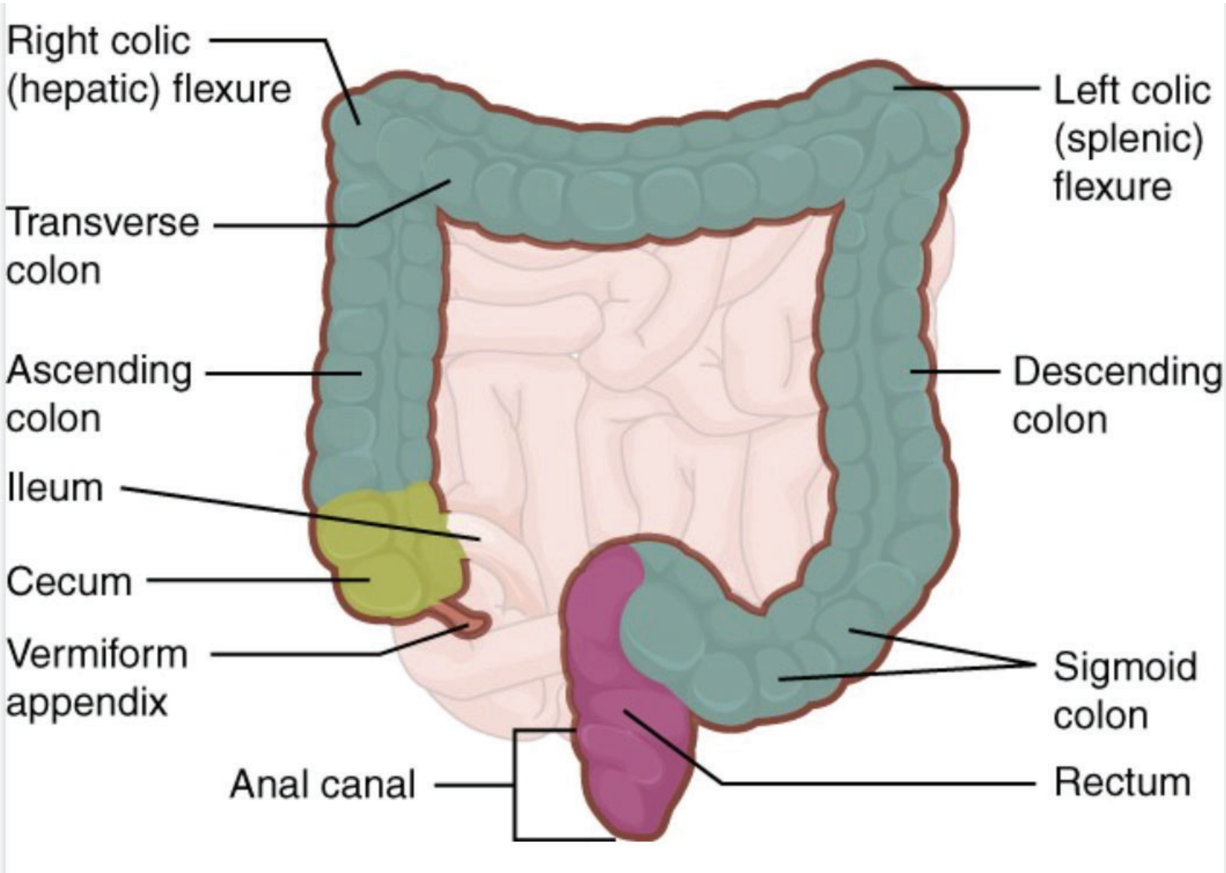
Insulin does far more than regulate blood sugar. Scientific studies show that nearly all our organs have specialized cells with insulin receptors. The brain and the placenta probably have the highest percentage of cells with significant numbers of insulin receptors. When insulin molecules bind to receptors, they signal the cell that all is well and that the cell should carry on with all its important functions at full capacity. However, when this signaling is blocked, our cells fail to be fully functional, and the cells neglect some of their important duties. If this goes on for weeks, months, or years, untoward things happen that lead to chronic disease. This is known as insulin resistance.

Over the last 15 years the long sought-after cause of the metabolic syndrome and many other chronic conditions has finally been uncovered. We now know that insulin resistance plays a major role in many chronic diseases. With these discoveries, a much better understanding of the underlying causes of so many chronic diseases are now being pursued. It is an exciting time in the understanding of so many diseases that effect our patients. It has completely upended traditional nutrition teaching.

The role of the colon microbiome

In the colon reside about a thousand different kinds of bacteria. It is estimated that as much as 100 trillion thriving bacteria live in our large intestine. This amounts to about 2.5 pounds of bacteria in the average adult. The bacteria make up about 60% of the stool. These bacteria are helping us to better understand why so many Americans have insulin resistance. It turns out that UPF, which nearly all Americans eat and drink (that our remote ancestors were not exposed to), are causing insulin resistance in several ways. Most Americans get most of their calories from UPF. It turns out that if one eats lots of UPF, the makeup of the bacteria (called the colonic microbiome) is significantly different than the bacteria in the intestines of folks who eat most of their calories from whole minimally processed plant food. This result has been confirmed now in hundreds of studies of the microbiome using DNA sequencing techniques to determine which bacteria predominate. We now know that a healthy microbiome that results from eating a lot of minimally processed whole plant food prevents and helps treat many chronic diseases. We also know that an unhealthy microbiome that results from eating UPF greatly increases the risk of getting one or more of these chronic diseases. Unhealthy microbiomes produce harmful metabolites in the colon and much less of the healthy metabolites that support a healthy lining to the colon. Because of this, the unhealthy microbiomes allow chemicals to get into our circulation that trigger insulin resistance.

Parts of the Large Intestine



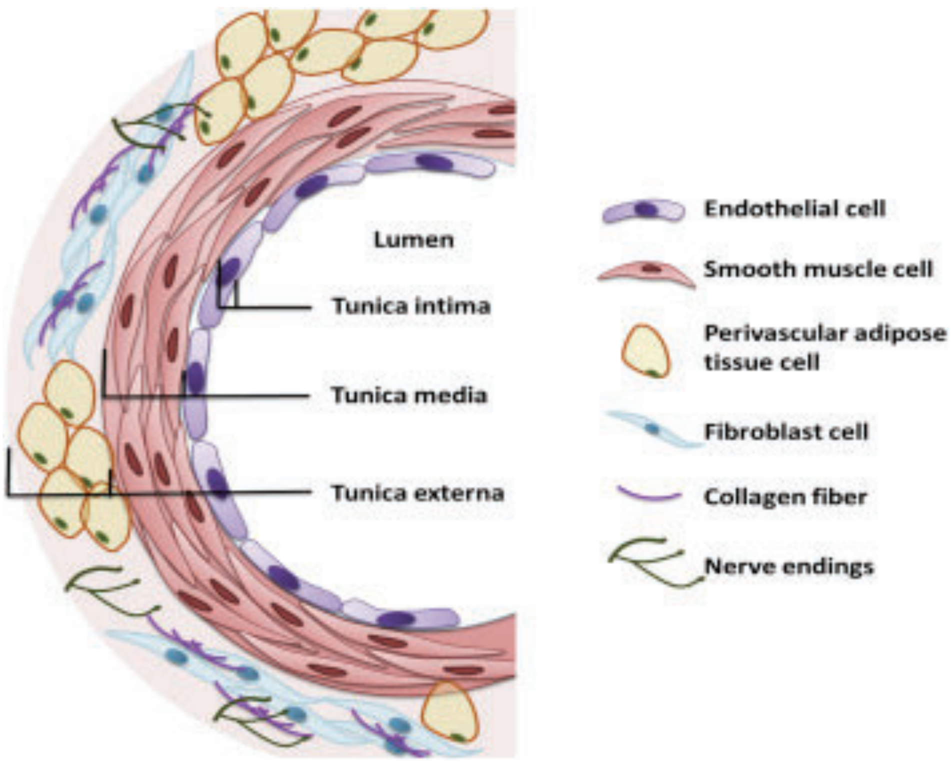
Hypertension

Most hypertension is caused by a combination of several things. Genetic makeup, stress, and lack of regular exercise play a role. Most importantly by far is UPF. In the face of no UPF and eating plenty of whole minimally processed plant food, even high risk, stressed individuals would have a much lower chance of getting hypertension.

In 1987 I attended the Montana Academy of Family Physicians education meeting at Fairmont Hot Springs near Anaconda. One of the speakers gave a talk on “Endothelial Cell Dysfunction” and how it was at the heart of most vascular diseases such as hypertension, stroke and coronary artery disease. Now, 30+ years later, scientists have shown how important endothelial cell dysfunction is in many diseases. They have found out what causes this dysfunction and validated how important it is to prevent it.

Endothelial cells perform critical functions in every organ system. They line all the arteries, arterioles, capillaries, venules, veins, all the placental vessels, lacteals of the intestines, lymphatic vessels, the inside of your heart, and the glymphatic system on the surface of the brain. Your blood pressure is controlled by the endothelial cells that line the arteries, arterioles and capillaries. Below is a cross section of an artery showing the endothelial cells on the inside of a blood vessel. These endothelial cells are responsible for telling the smooth muscle cells to dilate, lower blood pressure and improve blood flow locally. The endothelial cell releases nitric oxide to tell the smooth muscle to relax when there is more blood needed locally [25]. The sympathetic nervous system ("Nerve endings" in the diagram) tells the smooth muscles when to constrict which raises blood pressure and reduces blood flow.

Cross Section of an Artery



Besides controlling blood pressure, the endothelial cells of the arterial system do several other important things [24].

1. When you cut your finger, these cells get very busy locally.
   a) They release molecules that stimulate clotting to stop the bleeding.
   b) They tell the blood vessels to form new tiny blood vessels to supply the injured area (angiogenesis).
2. They can sense infection in the blood stream (such as in sepsis) and tell your brain and immune system to get busy to fight the infection.
3. When healthy, they keep out substances such as cholesterol laden LDL particles and help prevent atherosclerosis. When unhealthy or dysfunctional, they facilitate the transport

of LDL particles into the artery wall, causing atherosclerosis such as coronary artery disease [49].
4. They provide a smooth surface for the blood to flow through.
5. They regulate local blood flow in addition to regulating blood pressure.

Dozens of scientific studies both in laboratory mammals and humans have shown a very high correlation of the UPF diet to endothelial cell dysfunction and the consequences of it, such as coronary artery disease, hypertension, DVT, pulmonary emboli, strokes and claudication [21-25]. Most importantly, groups of people who eat little UPF and mostly eat whole minimally processed foods have amazingly good blood pressures that do not increase with age. For example, I had high blood pressure as a teenager and into my early 20s. Blood pressure readings when I was in medical school were as high as 160/110. I did some reading of articles then and decided to cut out salty foods and keep my sodium intake quite low in the 500-1500 mg range. Within two months my BP was normal but not low. Because of a dairy allergy and prostate problems, I have been off dairy and red and processed meat for several years. Then, about a year ago, I finally decided to cut out sugar. Now about 80% of my calories come from minimally processed whole plant food. 3 months later at my annual checkup my BP was down to 102/60.

What is it about UPF that triggers endothelial cells to malfunction? There is always more to learn but below is a list of things we know that link UPF to endothelial cell dysfunction and subsequent hypertension.

The fructose story and how it differs from how we metabolize glucose [26-28]: Fructose is found in natural plant food (not found in natural animal-based foods). It is highest in sweet natural foods such as sweet fruits, honey, real maple syrup, sugar cane, and sugar beets. The sugar in your pantry (white or brown sugar) is nearly 100% sucrose. Sucrose is a glucose molecule and a fructose molecule bonded together. In otherwards, sugar (sucrose) is half fructose. Sucrose in UPF and drink is rapidly split into glucose and fructose in the upper small intestine and then transported to the liver. Another large source of fructose consumption in America comes from high fructose corn syrup, which is 50-65% plain fructose which directly enters the small intestine and goes straight to the liver. A third source is fruit juice. This was thought to be a healthy drink in the past but now, with what we have learned from studies on insulin resistance and fruit juice, we know that fruit juice is just as unhealthy as soda pop due to the high unbound fructose content [29, 30]. Fruit juice has had the fiber matrix removed so the fructose is free standing and, like the fructose in high fructose corn syrup, is rapidly absorbed in the proximal small intestine and then into the portal circulation.

It is estimated that fructose consumption of the average American is at least 50 to 100 times higher than that of our remote ancestors. Consumption of fructose, mostly in the form of sugar, remained low until the late 1700s when it started going up with the sugar trade. Sugar consumption in America on average was about a teaspoon a day per person in 1700, about 5 teaspoons a day in 1800, 28 teaspoons in 1900, and by 2000 was about 56 teaspoons a day. High fructose corn syrup was introduced in the 1970s and by the 1980s was common. As you can see, fructose consumption had been very low until the last 130 years. There has not been time for the human cells to change how they metabolize and utilize fructose in such large quantities.

Most organs in your body have cells that absorb fructose. Liver cells absorb the most. The liver processes about 70% of this excessive amount of fructose. How it is processed has mostly been worked out.

First, we will compare glucose with fructose processing by your cells [31, 32]. The liver gets one of its favorite substances, glucose, from starch found in essentially all minimally processed plant food. It also gets glucose from the break down of sugar. Only about 20% of the glucose you get from a meal is processed by the liver. Nearly all your cells utilize and can take up glucose for energy as they need it. The liver and other cells regulate how much glucose they bring in. A small amount of the glucose that enters the liver cell is broken down into energy (ATP) and citrate by the mitochondria. Most of the glucose that is absorbed is stored within the liver cell in the form of glycogen that can quickly be broken down into glucose and released in your circulation when you need it. When your cell has had enough glucose, it reduces or turns off the absorption of glucose. Also, if the cell has enough ATP for energy and/or citrate is accumulating, it turns down or off the production of ATP, citrate, and the storage of glucose as glycogen. Almost all other cells in your body break down glucose into energy (ATP) but only liver and muscle cells store glycogen. Only the liver releases the glycogen into your circulation as glucose. Muscle glycogen is used mostly when you are exercising.

How is the processing of fructose different? Like glucose, when fructose is absorbed into your circulation it goes into the portal vein which first sends the blood to the liver. The liver takes up most of the fructose into its cells, but, unlike glucose, it has no way turning off the absorption. There is no feedback to tell the cell it has had enough fructose, so it keeps absorbing the fructose when it shouldn't. Also the gradient of fructose concentration after a sugary meal remains high because when fructose enters the cell it rapidly is converted to fructose-1 phosphate keeping the intracellular concentration of fructose low. The cell must utilize ATP to convert the fructose to fructose-phosphate. The ATP used for this step is converted into ADP (goes from 3 phosphates to 2, hence the T to the D). The consequences are:

1. When there is too much ADP, it gets converted into uric acid. The uric acid accumulation also can occur in endothelial cells that line your arteries. When the endothelial cells accumulate uric acid, this blocks the release of local nitric oxide so the endothelial cells cannot dilate the artery very well and this leads to hypertension.
2. Back in the liver, the mitochondria get overwhelmed by the excess production of fructose-phosphate and ADP and produce too much citrate. Normally the citrate is metabolized mostly in the mitochondria. If the cell does not need the energy produced by the mitochondria, it turns off the metabolism of citrate and the mitochondria send the excess citrate back out to the cell cytoplasm. The liver cell must convert the excess citrate into fatty acids. Again, if there is too much of this, some gets turned into fat globules inside the liver cells. Also, some excess goes into your blood stream raising your triglyceride levels. The other cause of fat droplets in the liver cells and elevated

triglycerides in the blood stream is the excess fructose-phosphate that stimulates the production of free fatty acids in the liver cell.

3. The accumulation of fructose-phosphate causes the insulin signaling to malfunction leading to insulin resistance. Other free radical molecules accumulate that contribute to worsening insulin resistance and fat accumulation within the cell.
4. As fat in the liver cells accumulates, it can lead to fatty liver disease and even cirrhosis with liver failure. Currently in adults, fatty liver disease is a close second to alcoholic liver disease as the main cause of liver failure and the need for a liver transplant. Fat can also accumulate in muscle cells. This is diet related.
5. In non-liver cells, too much fructose can lead to insulin resistance with the accumulation of uric acid and too much fructose-phosphate. Endothelial cells that line our arteries have insulin receptors. When insulin binds these receptors, it signals the endothelial cells to function normally to keep our blood pressure in the healthy range. But with insulin resistance, the endothelial cells do not get the normal signaling from the receptors. The cells become ”dysfunctional” due to accumulation of uric acid and fructose-phosphate. Healthy endothelial cells get messages from our nervous system about pressure and flow of the blood stream and normally respond with an appropriate release of nitric oxide to keep our blood pressure in the normal range. With insulin resistance, the endothelial cells think our blood pressure is fine when in fact, it is too high.

Most hypertension is thus triggered by dysfunctional endothelial cells. Excess fructose is a big trigger of this dysfunction and is a big problem in the American diet. The reason whole fruit does not cause too much fructose to hit the liver and other cells in the body like the endothelial cells is:

1. Fruit has a lot less fructose per ounce of food than UPF.
2. The fructose is much more slowly absorbed because it is contained in the cells of the fruit that have not been crushed by our teeth. The stomach acid and our own enzymes cannot open these cells. It requires fiber eating bacteria to open these juice containing cells.
3. The bacteria in the small intestine (which are much less numerous than the bacteria in the colon) will break down some of the cells. Some of this fructose enters our circulation and some is consumed by the bacteria.
4. Much of the fructose in the fruit cells will reach the colon where the huge number of bacteria will consume the fiber and open the cells. A lot of this fructose will be consumed by bacteria and some will be absorbed. Comparing this to fructose from sugar or high fructose corn syrup that is fully absorbed by the small intestine, one sees that the fructose in whole fruit does not cause marked surges in the levels of fructose in our circulation. One aside about fructose. It is prized by the UPF and soda-pop industry because it is a lot sweeter than glucose. If it is used by itself without being in sugar or mixed with glucose, it causes cramping, bloating and diarrhea. Ingesting fructose without it being accompanied by glucose overwhelms the small intestine’s ability to absorb it and it upsets the small intestine and the colon.

Hypertension from endothelial cell dysfunction is exacerbated by insulin resistance. Insulin resistance is aggravated by excess fructose exposure but also by inflammatory metabolites from the colon that get into our circulation due to eating too much of our calories in UPF and drink. **We will discuss the insulin resistance resulting from these inflammatory metabolites below.** Simply stated, diets high in UPF cause overgrowth of unhealthy bacteria that release too much inflammatory metabolites into the colon. Too much of these abnormal metabolites get into our circulation causing insulin resistance in most of our organs. Insulin resistance has wide ranging effects on our organs as will be discussed in Session 2. This, in addition to fructose, greatly increases the risk of getting one or more of the chronic diseases.

The Salt – Hypertension story. As you probably know, there are conflicting reports about the dangers of salt and what a healthy amount of salt is. Keep in mind that our ancestral digestive track was not exposed to a high salt diet until more modern times. Overall, the more sodium you ingest per day the slightly higher your blood pressure will be. Most unbiased studies show this. However, we now have a much better idea of why studies are inconsistent. Nearly all the studies do not consider what diet people are on, only the sodium content. It turns out that if a person has insulin resistance that is affecting their kidney function (this is not unusual), the kidneys will not get rid of excess unneeded sodium like they should. They will hold back more than is needed. Let's say we have two identical people except one has insulin resistance that is affecting their kidneys and the other does not having insulin resistance. Now assume both people change to a high salt diet from a low salt diet. The one with the insulin resistance will have a greater increase in blood pressure and more sodium retention. In essence, if one is on a healthy diet with little UPF and plenty of whole plant food, your body can handle a little extra salt occasionally. Another problem with a high salt diet is that, by itself, it can change the microbiome composition to something that is not so healthy. So, we do not want to go hog wild with the salt. The current recommendation of 2,300 mg of sodium per day or less is ok because so many Americans have insulin resistance. The recommendation for those with cardiovascular disease is 1500 mg per day. Keep in mind the real culprit is UPF, not just the salt. What type of diet is best for treating hypertension? This was established in 1999 with the DASH study where the most effective diet had whole grains, vegetables, whole fruits, nuts, a little non red meat and low fat dairy and no UPF[130]. Since then, hundreds of studies have revealed why this diet not only prevents but also treats hypertension as well as many other chronic diseases.

One of the oldest defenses against getting one of the many chronic illnesses is something not discussed very much: Satiety.

Satiety is defined as that satisfied full feeling you get after eating healthy food that tells you that you are done eating and can get on with doing other things. Most Americans do not experience this much anymore because we seem to always include UPF into our meals. Americans on their typical UPF diet often lose the natural cycle of that mild full feeling (satiety) that alternates with hunger. I think a better description of the feelings people get on a UPF diet is going from an increasing craving to satisfying the craving with often other positive feelings entering the picture. For some who struggle the most with their weight, these cravings lead to marked overeating. Most Americans on the UPF diet, do not markedly overeat. Studies show they often eat a little bit more than they need causing their weight to slowly go up. The feelings they get with eating UPF vary. It can be any one or combination of the following: a brief buzz or high, happiness, relaxation, calmness, alertness, sense of indulgence and/or satisfaction. The problem is these feelings are very short-lived, often only 30-60 minutes before cravings come back. These cravings can interfere with our concentration at times.

For example, UPF could be part of the meal such as in ranch dressing, or in what we drink such as a coke, or could be the dessert such as apple pie and ice-cream. Satiety is pushed aside by UPF. Eating UPF often leads to the discussion in our brains of “Boy! I would sure like more of that, but should I?” often back and forth. Whereas, when not eating UPF but eating real, whole, minimally processed foods, we hardly notice the transition from our brains shifting from “pass the potatoes” to cleaning up after a meal and getting on with the day. Many times, as a child, I would eat dinner and, as I am finishing, suddenly my brain is elsewhere such as thinking of a variation on a game my friends and I invented outside. Normally satiety would remain in the background for several hours. Running back into the house an hour later to get something for our new game, I spot a plate of chocolate chip cookies! Suddenly my satiety is gone as my brain focuses on the cookies.

Food is central to living. It is complex and very important to us. Satiety and hunger are a “normal” part of the food cycle in healthy folks eating mostly minimally processed whole foods. Once irresistible UPF enters the picture, memories of irresistible foods and cravings dominate our thoughts. It was thought that hunger and satiety only involved a small part of the hypothalamus in our brain, but you do not have to be a neuroanatomist to realize that these feelings of hunger, satiety and craving, involve many parts of our brain. For example, they clearly have a lot to do with our senses of smell, taste, mouth feel, touch, sight, as well as sound. Food that we have eaten has been a part of many memories which involves many parts of our brains.

Science has clearly established that minimally processed plant-based diets are best at creating satiety and reducing or getting rid of cravings. They also are the best diets for preventing or treating insulin resistance. This happens short term on a day-to-day basis as well as long term. When science narrowed down what it is in plant-based foods that causes satiety, they consistently found that it was the natural fiber cell wall matrix found in all minimally processed plant food.

There are a lot of hormones involved in satiety/hunger such as GLP-1 (glucagon-like-peptide) that increases satiety, ghrelin that stimulates hunger, leptin that turns down hunger and many others that participate in our daily digestion of food. These hormones play an important role in the Gut-Brain Axis that controls our appetite and regulates the digestion and storage of food. There are many feedback loops that involve the stomach, small intestine and large intestine. These parts of the digestive system absorb and move along our partially digested food. Science is still trying to figure out all these regulatory mechanisms for the 100s of different eating scenarios we put our digestive system through. As an example, we will focus on GLP-1 because it is well studied, and frequently in the news. Several of GPL-1 analogs are approved by the FDA for treatment of type 2 diabetes, obesity, and other conditions such as prevention of heart failure.

Where is GLP-1 made? What causes it to be released from the L cells? What does it do once it is released from the L cells?

GLP-1 is produced by special cells in our upper small bowel and the colon, called L cells. GLP-1 is a short acting hormone due to rapid breakdown by the ubiquitous enzyme dipeptidyl peptidase 4 (DPP4). GLP-1, after being released, can directly stimulate nearby nerves which come from the vagus, the sympathetic and the parasympathetic nerves [33]. These nerves send messages to several parts of the brain that you are filling up. Satiety goes up and hunger declines. Some gets in the circulation and tells the cells in the pancreas to release more insulin and other hormones.

GLP-1 release begins in the small intestine when food is broken down into glucose, amino acids, and free fatty acids. Each of these directly stimulate the L cells in the small intestine to release GLP-1. This stimulates satiety in our brain. As the partially digested meal works its way through the small intestine, the absorption of the sugars, amino acids and free fatty acid diminishes along with the GLP-1 release.

As the digesting material is leaving the small bowel it enters the large intestine. The L cells of the colon do not respond directly to glucose, amino acids and free fatty acids as in the upper part of the small intestine. Instead, these specialized L cells respond to short chained fatty acids (SCFA). The most common SCFA are acetic acid (in vinegar), propionic acid, and butyric acid. The source of SCFA is from fiber in whole plant food, resistant starch and the small number of amino acids that are produced in the colon. Raw and minimally processed starchy vegetables such as potatoes, sweet potatoes, beans, rolled oats, corn and peas have resistant starch. Resistant starches are large chains of molecules composed of small glucose-like molecules that are connected by bonds which our human digestive enzymes cannot break down. Bacteria in our large intestine can break these down releasing SCFA. Cooking these starchy plant foods greatly alters the starch so that human enzymes can break it down. This is one of the reasons that the absorption of glucose from a hot baked potato rapidly raises the blood sugar. Eating the potato raw or partially cooked results in a much slower rise in glucose. It turns out that eating cooked potatoes after they have cooled also results in restoring some of the resistant starch to its original form so more of the starch requires bacteria to break it down. Most importantly however is the fiber as a source of SCFA. Fiber from whole plant food provides the vast majority of the SCFA in the colon.

If the diet contains a lot of whole minimally processed plant food, then satiety continues for several hours as the SCFA levels stay up in the colon as the bacteria break down the fiber. Then, as the bacteria are finishing off the fiber, the SCFA levels decline and hunger rises starting the cycle of eating over again with the next meal. Without fiber, not enough SCFA are produced and the brain thinks you are done digesting and hunger goes up sooner than it should.

How do GLP-1 analogs such as semaglutide and tirzepatide work?
These artificial analogs of GLP-1 work differently because, even though they are like the GLP-1 molecule, they have been modified so they are broken down in the circulation very slowly. Natural GLP-1 has only a 2-minute half-life. The analog GLP-1 drugs have a 6 to 7-day half-life and only require a once-a-week SQ injection or a once-a-day pill.

The problem with GLP-1 analogs being long acting instead of short acting:
In laboratory animals, when these drugs are injected into the CSF in the brain, the animals simply stop eating until they get rid of the drug. The brain cells of humans and lab animals are used to getting only very small amounts of GLP-1. The analogs of GLP-1 can easily overwhelm the GLP-1 receptors in the brain to the point that you don't feel like eating at all. These high levels can even stop your food cravings if taken in a high enough dose. In many people, before the appetite is completely turned off, they get nauseated and some vomit. Studies show that over half of users of these GLP-1 analogs stop the drug in a year or less. The most common reasons are nausea, vomiting, diarrhea, abdominal pains, cost and drug shortages. Data collected from prescribers show about 15% of people who try these drugs report they do not lose weight or lose very little. There have also been reports of people who stay on these drugs of losing their appetite for junk foods, especially sweet ones and favoring natural sweets such whole fruits. A large VA study showed that many of the chronic illnesses caused by insulin resistance seem to be reduced in people taking these analogs.

"Compared to usual care, GLP-1 analog use was associated with a reduced risk of substance use and psychotic disorders, seizures, neurocognitive disorders (including Alzheimer's disease and dementia), coagulation disorders, cardiometabolic disorders, infectious illnesses and several respiratory conditions.

It also showed significant side effects:
There was an increased risk of gastrointestinal disorders, hypotension, syncope, arthritic disorders, nephrolithiasis, interstitial nephritis and drug-induced pancreatitis associated with GLP-1 analog use compared to usual care." [61]

3 ways UPF annihilates satiety [34-36].

1. UPF has little or no fiber and has no intact cell wall fiber. The colon does not release enough GLP-1 because the levels of SCFA that stimulate GLP-1 release are too low. When the SCFA levels are low, the brain centers think your colon is done digesting and hunger goes up and satiety goes down. Another way of putting this is folks that eat lots of UPF are starving their colon of fiber.
2. UPF has a very negative effect on the make-up of the microbiome. Unhealthy bacteria that lead to an increase in the release of inflammatory metabolites increase in numbers. The lack of fiber matrix that is in whole plant food leads to low SCFA levels. The cells in the colon normally prevent the absorption of inflammatory metabolites when they are robust and dining on SCFA. When SCFA are scarce, these cells are unable to keep out the inflammatory chemicals. In addition to triggering insulin resistance, these inflammatory

metabolites can directly block the satiety centers and prevent the normal satiety-hunger cycle from functioning properly.

3. Often UPF lights up our reward center and takes over our brains. As in the childhood example above, suddenly the child is no longer thinking about the new game outside. His brain turns to the plate of chocolate chip cookies and satiety is suddenly gone. UPF triggers insulin resistance in many parts of the brain including the reward center. In healthy people without insulin resistance, insulin levels go up in the brain while eating and dopamine levels in the reward center drop. The reward center calms down. During studies, functional MRIs show the networks around these centers also quiet down. In people with insulin resistance, insulin does not work very well. The reward centers stay activated. Hunger and cravings do not subside or may even worsen. Satiety is not signaled. It has been well established in humans that many folks with insulin resistance on the UPF diet eat a little bit more than they need each day. This is one of the reasons many people with insulin resistance gain weight.

   A study done in 2008 at Pennsylvania State University [37] compared ingesting 125 calories of a pre-meal consisting of whole peeled apple, apple sauce, apple juice with fiber, or apple juice without fiber in 58 subjects over 5 weeks. The subjects did this for one meal a week and consumed one of the 4 pre-meals 15 minutes before their lunch. Lunch was typical UPF consisting of cheese tortellini (Ralzoni and Bros brand) and red sauce (Traditional Prego brand). **Overall, the whole apple increased satiety more than applesauce or apple juice. Adding naturally occurring levels of fiber to juice did not enhance satiety. These results suggest that whole fruit affects satiety more than pureed fruit or juice. Results showed that eating the apple reduced lunch energy intake by 15% compared to control ($p < 0.0001$) and decreased energy intake compared to applesauce and both juices. Simply stated studies show that we eat a few more calories per meal when UPF is involved. When we include a significant amount of whole plant food, it improves our satiety and reduces caloric intake.**

Craving and Addiction of Ultra Processed Foods – UPF

When stopping at a convenience store on a long road trip, what foods or drinks enter your brain? When passing through the employee lounge on the way to your desk in the morning, you noticed someone brought homemade cinnamon rolls. Later it’s morning break time and what is on your mind? Most of us can list at least a few things that are hard to stop eating once we start. Most of us have had times when we tried to cut down on certain foods or drinks. Many of us have had trouble ignoring cravings for certain food or drink items. These are all characteristics of an addictive substance.

The production of these addictive processed foods began over 200 years ago. For example, the production of sugar from sugar cane began in SE Asia around 4,000 BC. Widespread use of sugar as an additive really began with the spread of sugar cane cultivation from SE Asia to the Middle East, and then to West Indies. In the late 1600s sugar cane was one of the products shipped to

Portugal from the West Indies to be processed in factories into crystalline sugar. This gradually grew and by 1900 was a huge worldwide business. Many other processed foods began to appear in the 1800s and the food industry took off in the early 1900s. By the 1960s-70s most Americans were buying lots of UPF. Now it is estimated that 73% of food and drink on the grocery shelves is ultra-processed.

The food industries have hired scientists for more than a hundred years to perfect the taste of processed food and drink [38]. They have not done studies on the long-term harm of these foods and drinks before they are released to the public. The food industry continues to ignore and suppress what science has learned about their creations. Taste testing began years ago and even involved toddlers. Scientists learned what concentration of additives worked the best. For example, in a test on chocolate pudding the scientists varied the concentration of sugar and observed toddlers' reactions to determine what concentration was most appealing. It turns out they learned that kids' bliss point (point where the concentration of sugar was most irresistible) for sugar in the pudding was double that of adults.

In England Professor Chris van Tulleken, who has done children's and adult Broadcasts on BBC TV and radio, is a real advocate for eating whole minimally processed foods. In his book "Ultra-Processed People" he tells of doing an experiment on himself. He went completely off UPF for a month, then had a medical evaluation, and then switched to at least 80% of his calories as UPF for a month. Prior to the study his meals at home were healthy but did include some UPF. Embarking on his 80% UPF diet, he is at the breakfast table with newly purchased Cocoa Pops (similar to our Cocoa Puffs) and his 3-year-old daughter is eyeing the box of Cocoa Pops which has a cute, very appealing cartoon monkey on the box. Almost immediately, she demanded to try some. Tulleken refused and she turned into a screaming mass on the floor under the table. He persisted and ignored her while eating his own Cocoa Pops. While he was contemplating all this, he failed to notice his daughter had crawled up into her chair. When he realized she was back in her chair, he decided to watch as she poured a bowl full of Cocoa Pops. She was eating it by the handfuls with a crazed look on her face. He continued watching. As she continued to pour more into her now empty bowl, she seemed like she was in a trance! I had a similar experience with a newborn the first time I used a binky dipped in sugar water just before a circumcision. I had dragged my feet about giving newborns sugar, but the nurse convinced me to try it in this case when the baby would not quit screaming. I watched as she put the binky in his screaming mouth. In just a few seconds his eyes rolled back in their sockets. He quit screaming and went limp! I said to myself, "WOW! I just witnessed his first big high!"

There is little wonder why cravings and addiction play a significant role in overeating UPF and choosing it over real whole foods. Once your reward center kicks in, satiety goes out the window until all the homemade cinnamon rolls are gone [39].

What is all this talk and press about the microbiome?

In 2013 the results of a human twin/laboratory mouse study were published [40]. The results went viral around the world. The inescapable conclusion was that the microbiome causes obesity. Human stool from twins (one normal weight and one obese) when transplanted into sterile (no bacteria in their intestines) mice showed that stool from the normal weight twin did not change the weight of the mouse, but human stool from the obese twin consistently caused obesity. If the lean mice stayed on their healthy diet (lots of plant food) and the obese stool mice were put in with those lean stool mice, the obese mice gradually lost the weight. If their diets were switched to a UPF type diet, the obese mice did not lose weight.

Some studies of the human microbiome began several years earlier. When researchers began using DNA sequencing tools to look at the DNA of bacteria in our stool, they realized there was a gold mine of new information to be had. In the beginning, the realization was that there were a lot more unknown bacteria in our colons than known species. This research began slowly. After 2013 it basically exploded. We now know from these studies many new things about our amazing large intestine and its contents.

Scientists wondered if there was a pattern to the types and amounts of colon bacteria in people who are healthy compared to say someone with significant insulin resistance. Scientists who studied the stool samples of people with Type 2 Diabetes, hypertension, certain cancers, dementia, behavioral diseases, or autoimmune diseases were amazed how consistently different their pattern of bacteria were from the bacteria pattern in the colon of healthy folks.

This led scientists to coin a new term for unhealthy patterns of bacteria in our stool: <u>Dysbiosis</u>. This is now defined as a mixture of bacterium types that are harmful as opposed to a healthy mixture of bacteria that prevent chronic illness. Studies consistently show that whole minimally processed food diets produce mixtures of bacteria that keep us healthy. Changing to a diet with UPF and very little whole plant food causes the mixture of bacteria to become unhealthy.

What bacteria live off in the colon:

1. About 5% of <u>the food we eat,</u> makes it into the colon.
2. <u>Epithelial cells that are shed off the inside of the intestines</u> only live 2-3 days, and we shed billions of them every day.
3. <u>Dead bacteria & their cell walls</u>. This is very important as dead gram-negative bacteria cell walls are the main source of inflammatory metabolites such as lipopolysaccharides.
4. Most important for our health is the <u>fiber in whole plant food</u>. The healthy bacteria that collectively break down fiber into SCFA are essential for the health of the epithelial cells that line the colon and for signaling our brain about what is going on in the colon.

Fiber

Historically, the fiber hypothesis began in August 1953 when the British Medical Journal published an article by Eben H Hipsley M.B. B.S. from the Australian Institute of Anatomy [41]. Hipsley had done extensive research in various countries on the incidence of toxemia in relation to natural plant food diets as opposed to more processed western diets. He is credited with coining the term dietary fiber. He noted in Fiji that the natives ate most of their calories in natural plant food such as sweet potatoes, yams, brown rice, greens and others, whereas the Indian (from India) Fiji populations ate a diet very low in natural plant food. Hipsley noted that over a 3-year period, 1947-49, the incidence of toxemia in the Indian (India descendants) ranged from 2-6% of deliveries per year. The natives (descended from natives of Papua New Guinee) had no cases of toxemia those 3 years. Each group had over 700 deliveries. He also noted that in Sydney, Australia, toxemia was more common during the winter months when fruit and vegetables were scarce than the summer months from 1938 to 1945. Also, one of the highest rates of toxemia for the whole year was 1942 when there was a significant shortage of vegetables [42]. In 1975 HC Trowell from England furthered the "Fiber Hypothesis" when comparing English diets with that of Uganda. In his summary he stated, "A hypothesis has been proposed that dietary fiber-depleted starchy foods are conducive to the development of diabetes mellitus in susceptible human genotypes." [17]

Fiber is made of large complex molecules that make up the cell walls of plants. The bacteria in our intestines often work together to break down this fiber into much smaller molecules. As we discussed, bacteria in our colon survive on a variety of food sources. Breaking down substances in the intestines (especially in the large intestine) by the bacteria generates energy for the bacteria to grow and divide. This also produces breakdown products called metabolites. Some of these are harmful to us if they get into our circulation. Many of them are beneficial such as SCFA. One of the important jobs the colon is supposed to do is keep the harmful metabolites inside the colon so they pass out harmlessly in our stool.

How does dysbiosis (abnormal pattern of bacteria in the colon) cause illness? When a person eats most of their calories from UPF and very little from whole plant food (whole grains, vegetables, whole fruits and unprocessed nuts) it creates a perfect storm for harmful metabolites to get into our circulation and cause problems in many organs in our bodies. There are likely dozens of harmful metabolites. I will focus primarily on one of the most studied of these harmful metabolites: Lipopolysaccharides (abbreviated LPS) [137-139]. LPS is a large molecule on the outer membrane of pathogenic gram-negative bacteria. It is very immunogenic and plays a major role in gram negative sepsis. When dysbiosis is present the gram-negative bacteria whose cell walls break down and release LPS are present in much higher numbers than in the stool with a healthy microbiome. This makes it more likely that more LPS will sneak into the circulation and trigger inflammatory reactions in our cells that can lead to insulin resistance. In addition, dysbiotic stool has a lot less SCFA because of the lack of fiber in the diet. In this situation, the epithelial cells are weaker and less robust and have trouble keeping the LPS from getting into the circulation. Electron microscopy has shown that these weaker epithelial cells have much less of the tight bonds that hold the epithelial cells together. Also, gram negative bacteria secrete small spherical extracellular vesicles about 1/10th the size of a red blood cell. For unknown reasons this secretion increases on a UPF diet. These tiny spheres are secreted as a way for the bacteria to communicate with its neighbors. They contain a lot of LPS and may be the main reason LPS levels rise so much on a UPF diet.

How does UPF cause atherosclerotic vascular disease?

There are many steps involved when linking up vascular disease with UPF. Epidemiology, as discussed earlier, shows us that diets high in minimally processed plant food have very low rates of atherosclerosis. Conversely, more current population studies show much higher rates of vascular disease in people who eat lots of UPF. Many health care specialists believe that getting atherosclerosis is a normal part of aging. Some get it younger and worse than others. Epidemiology says otherwise. Studies after World War II showed a strong correlation between atherogenic diets (high in red meat, processed meat, dairy and sugar and low in whole plant food) and coronary disease. Research physicians in the 1950s in Europe realized that the rationing that occurred during the war provided an opportunity to see if it had an impact on coronary deaths [43-48]. Civilians had ration cards for meat, dairy (milk, butter and cheese), eggs and sugar. Their governments kept statistics on the usage of these cards. This occurred in Great Britian, Norway, Sweden, Netherlands, Belgium, Austria and others. Before 1960 it was commonplace for medical deaths to have autopsies. This provided accurate data of the incidence of serious coronary disease. From 1939 to 1945 there was a dramatic drop in coronary deaths that corresponded to the drop in consumption of meat, dairy, eggs, and sugar. There was one exception: Denmark did not ration dairy, especially butter. Denmark normally exported a large amount of butter, but this was disrupted during the war years. Butter consumption in Denmark went up during the war and unlike the other countries, coronary deaths did not go down but continued the steady increase in coronary deaths that had been happening since 1900.

The arterial endothelial cells we discussed are at the center of this issue. As mentioned before, they have several important things that they do. Besides regulating blood pressure and clotting, they also are responsible for keeping the cholesterol laden particles like LDL from getting into the arterial walls. Healthy endothelial cells do a good job of keeping out the LDL. In the face of lots of UPF with too many frequent bursts of fructose and exposure to inflammatory metabolites such as LPS, they become dysfunctional. In addition, erratic and/or very high blood sugars can cause endothelial cell dysfunction. The dysfunctional endothelial cells are unable to keep LDL from getting into the wall of the artery. In some cases, instead of keeping it out, they facilitate the entry of LDL and help pass it into the wall of the artery.

There is scientific evidence that healthy endothelial cells can also remove cholesterol from the wall of the artery and pass it back into our circulation [50]. Experiments on monkeys clearly showed that atherosclerosis is reversible over time [51]. Human studies looking at plaque frequency and thickness have also shown that with proper diet, with or without statins, atherosclerosis is at least partially reversible [52].

To summarize, UPF increases the frequency that high levels of fructose will get into the endothelial cells and cause the cells to misbehave. This misbehavior involves moving LDL into the wall of the artery and involves local clotting. A patient with a ruptured plaque and endothelial cell dysfunction is much more likely to get a clot that grows and occludes the artery causing a stroke or heart attack. The dysfunctional endothelial cells release clotting factors when they shouldn't.

UPF also creates an abnormal microbiome in the colon. The number of unhealthy LPS-releasing bacteria go up and the number of SCFA-releasing bacteria go down. There is too much LPS in the bowel and not enough SCFA to keep the epithelial cells healthy. The epithelial cells cannot keep all the LPS inside the colon so too much LPS gets released into the circulation. LPS has been shown to trigger endothelial cell dysfunction which increases the transport of LDL into the artery and increases the risk of getting an arterial clot. There is more to the story and more to learn in the future.

Microvascular Disease

How come the 9 veterans with heart disease in the VA study discussed earlier started improving their walking distance and speed in just 2-3 weeks on a healthy non UPF diet? Scientific studies show that reversal of atherosclerosis takes many months and even years. The reason these veterans improved so quickly is that the microvascular circulation, when switching to a plant-based diet, begins to improve in a few weeks. Opening up of the microvascular circulation is the most likely reason these 9 veterans improved so quickly. Studies done as early as 1965 showed microvascular constriction in the retina of 20 healthy volunteers after a fatty meal [53]. This was again documented in a study in 2018 using 10 healthy volunteers and looking at data before and after a fatty meal [54]. This study showed deformity and inelasticity of red blood cells, an increase in fatty monocytes in the circulation, and release of myeloperoxidase that constricted the arterioles in the micro-circulation.

An example of microvascular disease is heart failure with preserved ejection fraction (HFpEF) which has become one of the most common causes of acute pulmonary edema [55]. It also has been found to be the cause of ischemic looking exercise stress tests in people with angina and non-obstructive coronary arteries [136]. Microvascular disease also plays a role in other parts of our bodies [58]. In the brain, it is a significant contributor to dementia where it can cause small lesions in the subcortical white matter of the brain [57]. It likely contributes to reduced cognition in hypertensive teens as well as brain fog seen with chemotherapy and post COVID. In the legs, it plays a major role in triggering claudication symptoms. In the heart, it plays a role in angina patients where studies show about 30% of angina patients have microvascular constriction. Microvascular dysfunction also has been shown to be an important contributor to chronic renal disease and pre-eclampsia.

What happens in the microcirculation on the cellular level normally when we get physically active? All our blood vessels, including the tiny, microscopic arterioles have insulin receptors. When these are healthy and we start to exercise, the microcirculation "recruits" capillaries that are not being used. Dormant, unused capillaries open up and get to work to supply more oxygen to our heart, lungs and skeletal muscles. With insulin resistance, this process may not work as well, and the muscles do not get as much nourishment and oxygen as they need. This can contribute to fatigue, angina, claudication, or heart failure.

Here are some examples of capillary recruitment:

- Exercise: Before exercise, the small vessels in the lungs can't accommodate the increased blood flow needed for exercise, so the lungs recruit unused capillaries to handle the increased blood flow and oxygen needed. This helps keep pulmonary artery pressure from changing too much during exercise and provides more oxygen.
- Insulin: Insulin can stimulate capillary recruitment in skeletal muscle, which may help improve glucose delivery.

- Arterial tone: Changes in arterial tone can cause capillary recruitment.

Example of researchers ignoring nutritional treatment:
Coronary Microvascular Disease: Current Concepts of Pathophysiology, Diagnosis and Management, in Review Cardiovascular Endocrinology Metabolism. 2020 Jul 16;10(1):22-30. Lead author: Aish Sinha at Kings College London, England.
"Coronary microvascular disease (CMD) is present in 30% of patients with angina and is associated with increased morbidity and mortality. We now have an improved understanding of the pathophysiology of CMD and the invasive and noninvasive tests that can be used to make the diagnosis." Further: "Despite major advances in diagnosing and stratifying this condition, therapeutic strategies remain limited and poorly defined"

Many studies have shown that insulin resistance is caused by diets low in whole plant food and high in UPF, fatty meats and dairy as well as sugar [63]. Healthy diets with lots of whole plant food and little UPF improve insulin resistance [62], as well as improving flow mediated dilation (which is a way to measure how healthy the endothelial cells are working). These date as far back as the 1930s when this was indirectly noted by Himsworth in London and Rabinowitch in Montreal [18, 19, 60]. Further, microvascular disease has been shown to significantly improve on whole plant-based diets in patients with peripheral artery disease. [22, 23]

Given what you have learned, did changing the diet play a role in the rapid improvement of the 9 veterans in the Pritikin study in 1976? Is endothelial cell dysfunction reversible simply with diet? The science says yes.

Example of misleading or inaccurate comments found in my research:
"*While there is some evidence of a link between UPFs and poor health, there is not enough research yet to explain why*."
I see this kind of statement a lot in my readings of nonscientific news or internet articles. This was taken from a web site sponsored by Heart UK Cholesterol Charity. This is funded by the UK government and food companies such as ALPRO that makes highly processed food and drink products from plant foods such as vegan cheese and meat, soy milk such as Silk, non-milk-based yogurt and non-milk-based dark chocolate. Hopefully you can understand that this statement is not true. As shown in what I have presented so far, there is a tremendous amount of scientific evidence to explain why UPF is unhealthy and why whole plant-based foods are healthy and help prevent and treat common chronic diseases.

Vascular Complications of Pregnancy: Gestational Hypertension and Pre-eclampsia
As mentioned previously under the **Fiber** heading, as early as 1953 toxemia was likely shown to be caused by lack of fiber foods such as vegetables, whole fruit and whole grains. Studies looking at UPF diets especially containing fatty meats, butter, lard, palm oil, coconut oil, and cheeses show a significant increase in the risk of getting hypertensive disease in pregnancy [59].

Studies also show that the worse the insulin resistance or endothelial cell function is before pregnancy, the greater the chances are of getting pre-eclampsia or hypertension in pregnancy. [56, 64-66].

How does UPF, insulin resistance and endothelial cell dysfunction increase the risk of gestational hypertension? Blood pressure in pregnancy can go up with increasing insulin resistance. Studies show insulin resistance goes up more in pregnant women who have significant insulin resistance before they get pregnant.

Through the effects of fructose on the endothelial cells, and especially the effects of an abnormal microbiome in the colon releasing harmful substances like LPS into the circulation, insulin resistance causes the endothelial cells to malfunction. They then cannot carry out their normal duties correctly such as keeping the blood pressure in the normal range. This coupled with increased blood volume and placental factors of pregnancy contribute to hypertension in pregnancy. Hypertensive disease in pregnancy seems a lot more common now than it was in the 1970s [71].

Now let's look at the evolution of early and late pre-eclampsia. Insulin plays a big role in signaling a wide variety of cells in the developing pregnancy. Proper insulin signaling is critical for implantation as well as placental development and support throughout the pregnancy. In addition to the very numerous endothelial cells that line the uterine and spiral arteries and veins, insulin receptors are prominent on syncytiotrophoblasts and cytotrophoblasts that differentiated from the trophoblast cells that line the outside of the blastocyst stage of early pregnancy. The trophoblast cells invade the uterine lining and begin the placentation process. Syncytiotrophoblasts form the chorionic villi that get surrounded by maternal blood and exchange gases and nutrients with the developing fetus. The cytotrophoblasts are key cells in the formation of the invasion of the endometrium, spiral artery formation that supply the maternal blood, and anchoring the placenta to the uterine wall. Special macrophages and decidual stromal cells also have lots of insulin receptors and play a critical role in the ongoing development and maintenance of the placenta.

When there is significant insulin resistance at the beginning of pregnancy, there is a lack of necessary signaling of a variety of cells necessary for healthy placental development. Without signaling from insulin, these cells get dysfunctional and may not properly do their job. This can lead to miscarriage or hypertensive disease from abnormal development of the placenta. This can progress to early onset pre-eclampsia (before 37 weeks). If insulin resistance is worse during the latter half of pregnancy, this can lead to pre-eclampsia after 37 weeks or postpartum.

Gestational Diabetes

Most of us know that insulin requirements go up during pregnancy. It turns out that in women with insulin resistance, insulin requirements go up higher than women without insulin resistance. Insulin resistance not only is the main cause of type 2 diabetes but also is the main cause for gestational diabetes. Red meat, processed meat, and cheese along with UPF significantly increase the risk of getting gestational diabetes [67]. Within 5 years of starting universal screening for gestational diabetes in my office, I began doing a brief dietary history. I offered my pregnant mothers with abnormal 1 hour glucose screens a choice between doing a 3-hour GTT or seeing the dietitian and checking their sugars at home. Nearly all of them chose seeing the dietitian and checking their blood sugars at home. I think they knew that they were consuming too much unhealthy foods and drinks.

As we have shown, a diet based mostly on minimally or unprocessed whole plant food improves or eliminates insulin resistance. This significantly reduces the chances of getting gestational diabetes, gestational hypertension and pre-eclampsia.

Pre-pregnancy exercise has also been shown to reduce the incidence of these pregnancy complications likely again from its ability to improve insulin resistance throughout the body.

In the last few years of my practice (2017 to 2020), three women developed sudden onset postpartum pulmonary edema, needed to be hospitalized, and received IV Lasix. All 3 had normal cardiac echocardiograms. I had heard of pregnancy related pulmonary edema before but had never known any physicians who had seen a case. This struck me as very odd. Why was there a cluster of cases in Libby? A literature search was not fruitful. It mostly discussed abnormal cardiac echocardiograms. It is not a stretch to assume that these types of cases are happening in other parts of the U.S. All 3 of these cases involved three things which are not rare: minimal blood loss with their births, IV fluids, and use of Ibuprofen postpartum. But in the back my mind was that something had to be wrong with their hearts before this happened. I did not have a good answer. None were athletic and likely ate the typical American diet during their pregnancies.

Knowing what I know now, I think that the pulmonary edema could have been caused by their capillaries not opening in the heart and/or pulmonary vessels when they should have because of endothelial cell dysfunction caused by insulin resistance. Along with the fluid overload caused by lack of blood loss, IV fluids and Ibuprofen, insulin resistant microvascular dysfunction in the lungs and/or heart likely triggered marked increase in capillary wedge pressure which led to fluid buildup in the interstitial spaces and triggered pulmonary edema.

We know that preeclampsia involves retinal vessels, liver vessels, brain vessels, and/or kidney vessels especially at the microvascular levels [68-70]. These are all organs which are susceptible to insulin resistance. When the placenta malfunctions and releases sFlt-1 (soluble fms-like tyrosine kinase-1) and endoglin (sEng) which inflame the endothelial cells even more, these organs' endothelial cells in the microvasculature swell, leak fluid into the organ, cause swelling and loss of function, micro-clots and small infarcts. This can lead to visual problems that can persist for up to a year after the event, stroke, seizures, hepatic rupture and reduced kidney function. Women who suffer pre-eclampsia have a lifelong increased risk of vascular disease.

"*By contrast, the prediction of term and postpartum pre-eclampsia is limited and there are no preventive treatments*." From the Abstract in the 2023 article of *Nature Reviews Disease Primers* volume 9, Article number: 8 (2023)

These types of statements in well-respected texts and journal articles should no longer surprise me. But they still do. There are a large number of articles on pre-eclampsia clearly showing that insulin resistance and many chronic conditions caused by insulin resistance such as hypertension, obesity and type 2 diabetes significantly increase the risk of early and late pre-eclampsia. Science has shown that insulin resistance is reversible as well as many of its consequences such as endothelial cell dysfunction. Yet ACOG fails to actively promote dietary and exercise prevention in women of a fertile age. With about 40% of adults showing insulin resistance in the U.S., we should be including dietary and exercise prevention as part of routine women's heath care.

There are a lot more people trying to get the message out that non UPF, whole plant-based diets for women before and during pregnancy are the best way to have a healthy pregnancy and healthy baby. When we put together what we know about the microcirculation and about our knowledge of common pregnancy complications, the studies showing increased incidence of these problems in moms who eat and drink a lot of UPF make a lot of sense. We need to get rid of all the hype about dietary and supplemental gimmicks that are in the media and get back to basics of promoting unprocessed plant food and tell the truth about the harms of UPF. Unfortunately, researchers and organizations are afraid to speak up for fear of being sued, doxxed, or blacklisted by the food industry for disparaging their products. For example, Oprah Winfrey was sued by the Texas Cattlemen for $10 million dollars for making a single comment about eating hamburger. She had the resources to defend herself unlike most of us. She did win the case after 20 months of legal wrangling and a jury trial in Texas.

For some recipes that are tasty and high in whole plant food and low in UPF, please see the PDF document prepared by my wife entitled: "Recipes We Like". Another source of recipes is Forks over Knives.

Please answer the questions for this session. We will go over some of them before breaking into small groups in the first CME session for this topic. In the small groups of 3-5 people, you will be given a list of questions and tasks about a patient scenario to solve collectively and be ready to discuss your recommendations and answers in the last half hour of the session.