Casual Friday Series

The Layers of Liver Disease

A Biogenetix Clinical Presentation

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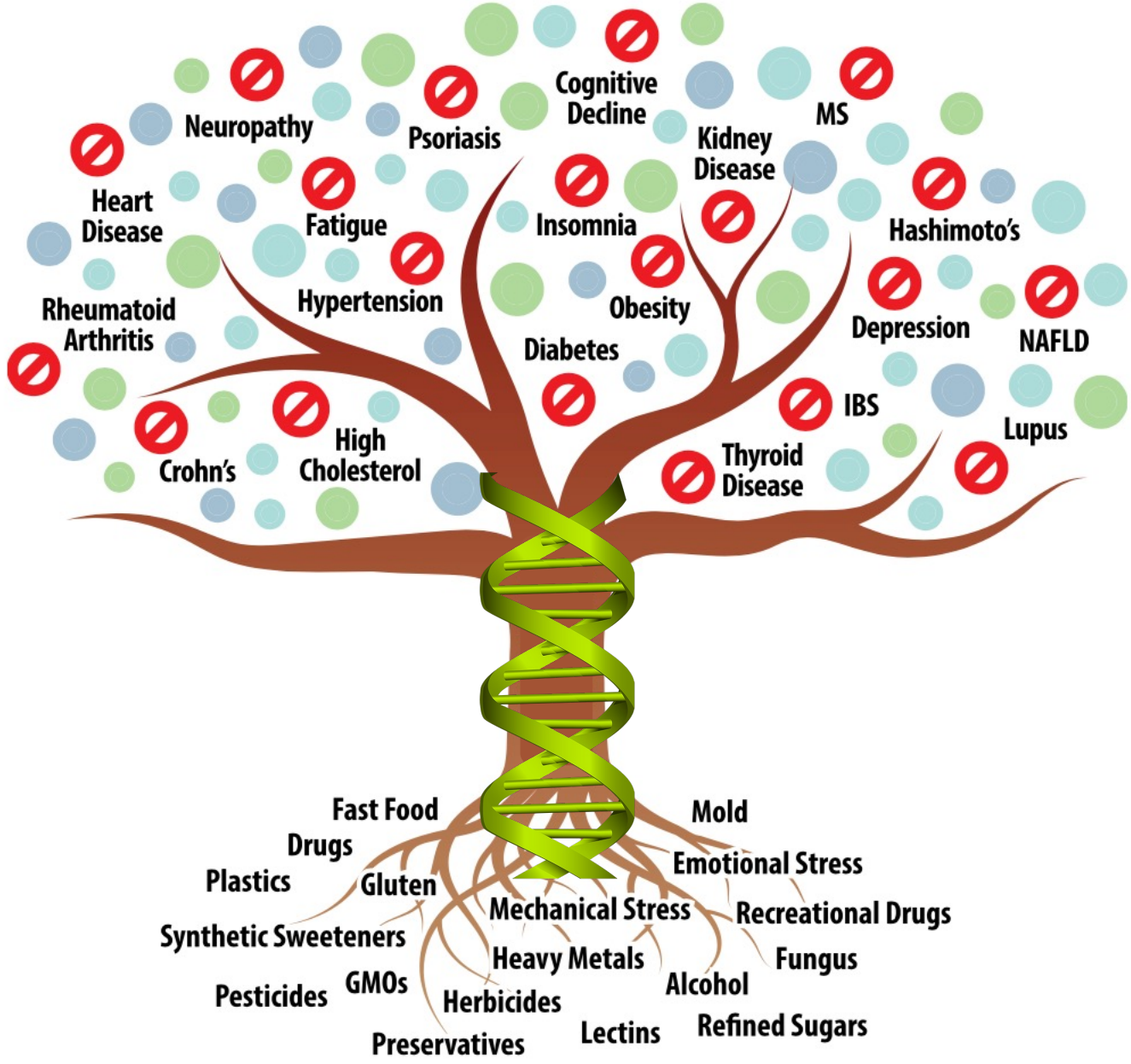
Neuropathy
Psoriasis
Cognitive Decline
MS
Kidney Disease
Heart Disease
Fatigue
Insomnia
Hashimoto's
Hypertension
Obesity
Depression
NAFLD
Rheumatoid Arthritis
Diabetes
IBS
Lupus
Crohn's
High Cholesterol
Thyroid Disease
Fast Food
Mold
Drugs
Emotional Stress
Plastics
Gluten
Mechanical Stress
Recreational Drugs
Synthetic Sweeteners
Heavy Metals
Fungus
Pesticides
GMOs
Herbicides
Alcohol
Lectins
Refined Sugars
Preservatives

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Burden of liver diseases in the world

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Affiliations + expand

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Abstract

Liver disease accounts for approximately 2 million deaths per year worldwide, 1 million due to complications of cirrhosis and 1million due to viral hepatitis and hepatocellular carcinoma. Cirrhosis is currently the 11th most common cause of death globally and liver cancer is the 16th leading cause of death; combined, they account for 3.5% of all deaths worldwide. Cirrhosis is within the top 20 causes of disability-adjusted life years and years of life lost, accounting for 1.6% and 2.1% of the worldwide burden. About 2 billion people consume alcohol worldwide and upwards of 75 million are diagnosed with alcohol-use disorders and are at risk of alcohol-associated liver disease. Approximately 2 billion adults are obese or overweight and over 400 million have diabetes; both of which are risk factors for non-alcoholic fatty liver disease and hepatocellular carcinoma. The global prevalence of viral hepatitis remains high, while drug-induced liver injury continues to increase as a major cause of acute hepatitis. Liver transplantation is the second most common solid organ transplantation, yet less than 10% of global transplantation needs are met at current rates. Though these numbers are sobering, they highlight an important opportunity to improve public health given that most causes of liver diseases are preventable.

The liver has a significant role in metabolism, regulation of red blood cells (RBCs) and glucose synthesis and storage. The liver function tests typically include alanine transaminase (ALT) and aspartate transaminase (AST), alkaline phosphatase (ALP), gamma-glutamyl transferase (GGT), serum bilirubin, prothrombin time (PT), the international normalized ratio (INR) and albumin. These tests can be helpful in determining an area of the liver where damage may be taking place and depending on the pattern of elevation can help organize a differential diagnosis. Elevations in ALT and AST in disproportion to elevations in alkaline phosphatase and bilirubin denotes a hepatocellular disease. Whereas, an elevation in alkaline phosphatase and bilirubin in disproportion to ALT and AST would denote a cholestatic pattern. The actual function of the liver can be graded based on its ability to produce albumin as well as vitamin K dependent clotting factors.

https://www.ncbi.nlm.nih.gov/books/NBK482489/

Quick Review:

Typically when reviewing LFTs, the discussion includes alanine transaminase (ALT) and aspartate transaminase (AST), alkaline phosphatase (ALP), gamma-glutamyl transferase (GGT), serum bilirubin, prothrombin time (PT), the international normalized ratio (INR) and albumin. These tests can be helpful in determining the area of hepatic injury, and the pattern of elevation can help organize a differential diagnosis.

The term "liver function tests" is a misnomer as many of the tests do not comment on the function of the liver but rather pinpoint the source of the damage. Elevations in ALT and AST in out of proportion to ALP and bilirubin denotes a hepatocellular disease. Whereas an elevation in ALP and bilirubin in disproportion to ALT and AST would denote a cholestatic pattern. The actual function of the liver can be graded based on its ability to produce albumin as well as vitamin K dependent clotting factors.[1][2][3]

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Elevated LFTs are found in approximately 8% of the general population. These elevations may be transient in patients without symptoms, with up to 30% elevations resolving after 3 weeks. Thus, care should be taken when interpreting these results to avoid unnecessary testing.[4][5]

Differential Diagnosis Based on Elevated LFTs

Hepatocellular pattern: Elevated aminotransferases out of proportion to alkaline phosphatase

- ALT-predominant: Acute or chronic viral hepatitis, steatohepatitis, acute Budd-Chiari syndrome, ischemic hepatitis, autoimmune, hemochromatosis, medications/toxins, autoimmune, alpha1-antitrypsin deficiency, Wilson disease, Celiac disease
- AST-predominant: Alcohol-related, steatohepatitis, cirrhosis, non-hepatic (hemolysis, myopathy, thyroid disease, exercise)

Cholestatic pattern: elevated alkaline phosphatase + GGT + bilirubin out of proportion to AST and ALT

- Hepatobiliary causes: Bile duct obstruction, primary biliary cirrhosis, primary sclerosing cholangitis, medication-induced, infiltrating diseases of the liver (sarcoidosis, amyloidosis, lymphoma, among others), cystic fibrosis, hepatic metastasis, cholestasis
- Non-Hepatic causes of elevated alkaline phosphatase: Bone disease, pregnancy, chronic renal failure, lymphoma or other malignancies, congestive heart failure, childhood growth, infection, or inflammation

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Cholestasis Labs

Alkaline phosphatase is part of a family zinc metalloenzymes that are highly concentrated in the microvilli of the bile canaliculus as well as several other tissues (e.g., bone, intestines, placenta). During growth, due to increased osteoblastic activity, elevated levels of ALP are seen in children and adolescents. The normal reference range levels also increase with age in females. Glycoprotein gamma-glutamyltransferase (GGT) is located on membranes of cells with high secretory or absorptive activities. Its main function is to catalyze the transfer of a gamma-glutamyl group from peptides to other amino acids. It is also abundant in many other sources of the body (kidney, pancreas, intestine, and prostate, testicles, spleen, heart, and brain) but is more specific for biliary disease when compared to alkaline phosphatase because it is not present in bone. The levels of GGT are higher in infants.[8]

Bilirubin is the end result of heme catabolism, with 80% being derived from hemoglobin. Unconjugated bilirubin is transported to the liver loosely bound to albumin. Bilirubin is water-insoluble and cannot be excreted in the urine. Bilirubin that is conjugated is water-soluble and appears in the urine. It is conjugated in the liver to bilirubin glucuronide and subsequently secreted into bile and the gut respectively.

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Functional Lab Ranges

- Alanine transaminase: 10-26 IU/L
- Aspartate transaminase: 10-26 IU/L
- Alkaline phosphatase: 65-90 IU/L
- Gamma-glutamyltransferase: 10-26 IU/L
- Bilirubin: .5-.8 mg/dL
- Prothrombin time: 10.9 to 12.5 seconds
- Albumin: 4.2-4.7 g/dL

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Alcohol

In patients with alcohol use disorder, AST to ALT ratio is generally at least 2:1, showing a high level of AST activity in alcoholic liver disease. Elevated GGT along with AST also suggests alcohol abuse.[9] GGT should not be used alone since it is not very specific for alcohol.[5]

Medications

Several medications are known to cause liver damage. Many of these are commonly used in daily practice, including but not limited to NSAIDs, antibiotics, statins, anti-seizure drugs, and drugs for tuberculosis treatment. Acute hepatocellular injury can be seen secondary to several drugs including but not limited to acetaminophen,[10] allopurinol, NSAIDs, alcohol, anti-tuberculosis medications such as isoniazid, pyrazinamide, and rifampin, statins, antifungals such as ketoconazole, antibiotics such as tetracyclines, anti-seizure medications such as valproic acid and phenytoin, antidepressants such as fluoxetine, antipsychotics such as risperidone and antivirals such as valacyclovir and ritonavir. Acute cholestasis can be seen secondary to drugs including anabolic steroids, NSAIDs, tricyclic antidepressants, alcohol, antibiotics such as azithromycin, amoxicillin, nafcillin, rifampin, and trimethoprim-sulfamethoxazole. Long-term use of these agents can also lead to chronic hepatocellular and/or cholestatic liver damage. Methotrexate, he commonly used medication for rheumatoid arthritis and other inflammatory arthritis can cause a mild transient elevation in LFTs and can also cause permanent liver damage in liver fibrosis and cirrhosis, especially with higher cumulative doses. Liver fibrosis can also be seen as secondary to chronic alcohol intake or methyldopa. Ergot alkaloids can result in ischemic necrosis. Oral contraceptives can result in hepatic venous outflow obstruction (Budd-Chiari syndrome). Herbal medications can also cause an elevation in LFTs.

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Viral Hepatitis

Viral illnesses are a common cause of hepatitis and elevation in LFTs. Viral hepatitis B, C, and D can cause chronic hepatitis, while hepatitis A and E cause acute viral hepatitis. Several other viruses, including HIV, Epstein-Barr (EBV), and Cytomegalovirus (CMV), can also cause hepatitis.[11]

Autoimmune Hepatitis

Autoimmune hepatitis is a chronic disease that is characterized by continuing hepatocellular inflammation and necrosis and a tendency to progress to cirrhosis. It is more common in young women than men with a 4:1 ratio. The patient usually presents with high LFTs without apparent cause. These patients can have positive autoantibodies, including antinuclear antibody, anti-smooth muscle antibody, anti-liver/kidney microsomal antibodies, and antibodies to the liver antigen.

Hepatic Steatosis and Nonalcoholic Steatohepatitis

Fatty liver disease, aka nonalcoholic steatohepatitis, has gained more attention recently because of its ability to cause chronic hepatic disease as well as hepatocellular carcinoma (HCC). The typical patient with this disease is overweight, has type II diabetes, or has dyslipidemia and no evidence of clinically significant alcohol use. The AST and ALT are usually both elevated with a ratio of 1:1, with other liver function tests being normal.

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Hemochromatosis

Hemochromatosis is the abnormal accumulation of iron in parenchymal organs, leading to organ toxicity. It is the most common autosomal recessive genetic disorder and the most common cause of severe iron overload. Clinical manifestations include diabetes, liver disease, and cutaneous hyperpigmentation. A raised serum ferritin level usually raises concerns for possible hemochromatosis, but a transferrin saturation greater than 45% is more reliable. HFE mutations (C282Y, H63D) are pivotal for the diagnosis of hereditary hemochromatosis. Secondary hemochromatosis can also be seen due to increased iron intake.

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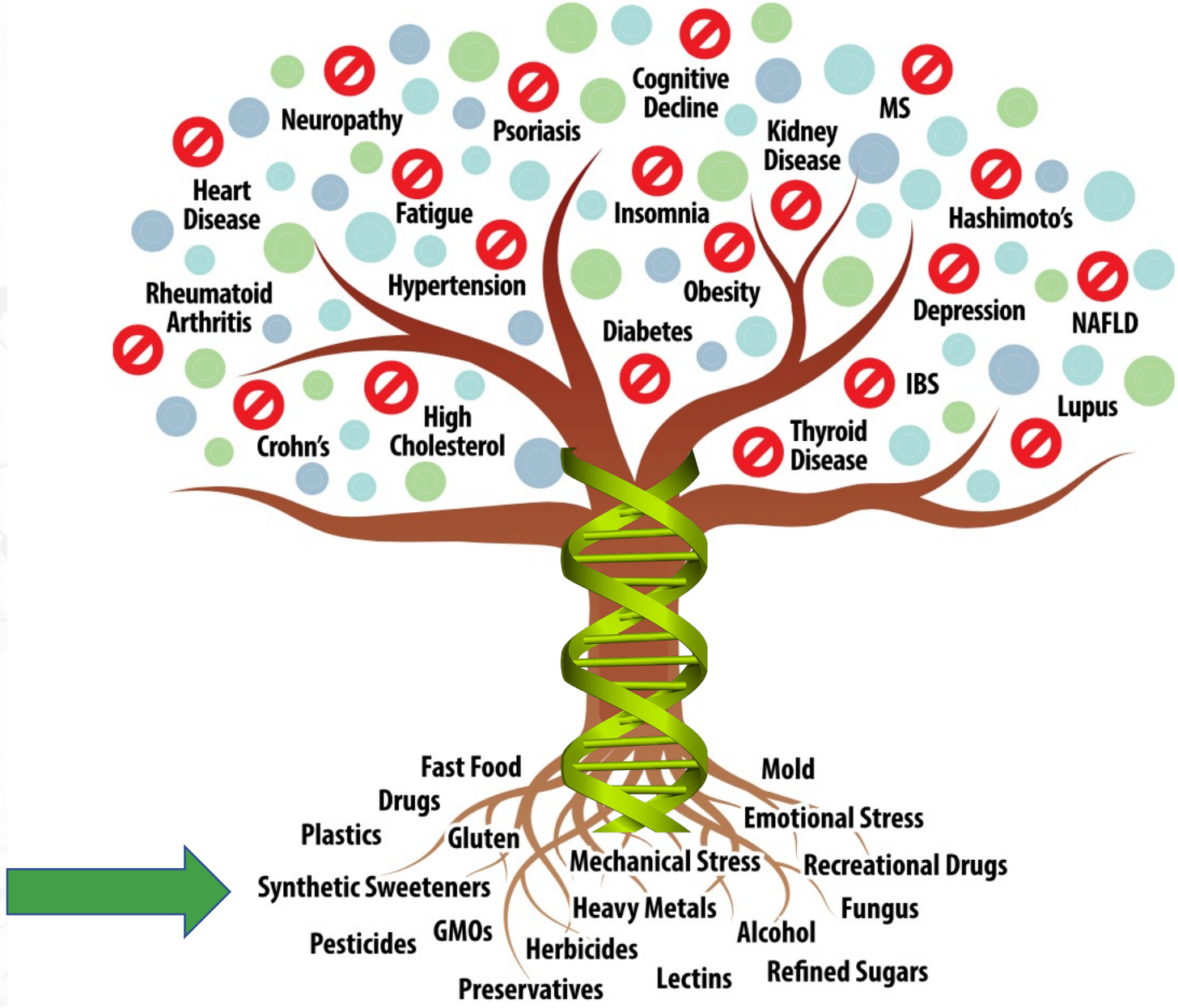
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Alcohol
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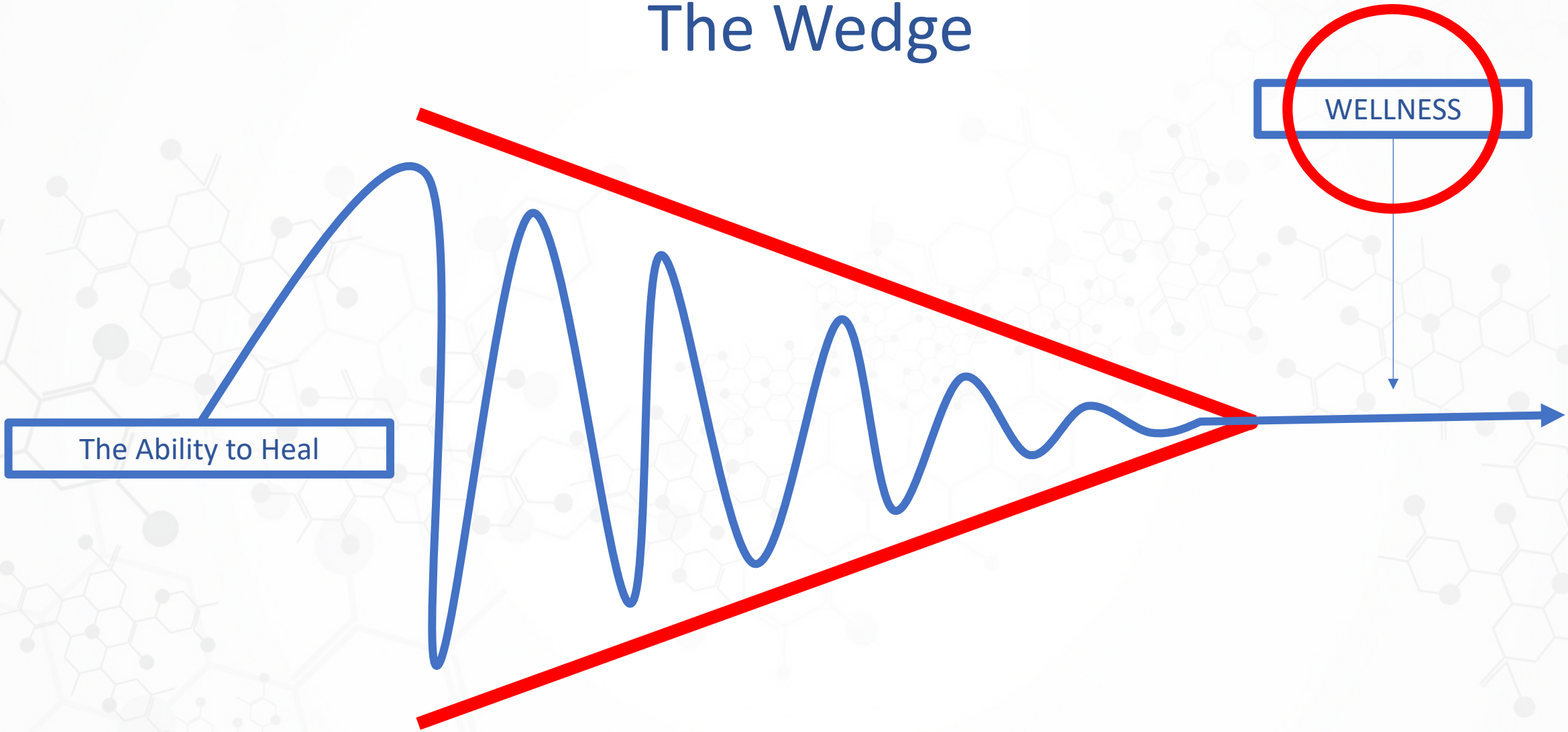
Refined Sugars
Preservatives

The Wedge



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