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**QUESTION 1:**

Like any organ, the liver requires a constant flow of blood to maintain life. The liver has a dual blood supply derived from the portal vein and the hepatic artery. The portal vein is a blood vessel that delivers blood to the liver from the stomach, intestines, spleen, and pancreas. Most of the liver’s blood supply is delivered by the portal vein. 75% of its blood comes in through the portal vein system, which is responsible for providing much of the liver’s oxygen and nutrients. The portal vein and its tributaries carry blood to the liver first, allowing the liver to process nutrients and neutralize toxins before they pass on to the rest of the body.

Blood leaves the liver through the hepatic veins. This blood is a mixture of blood from the hepatic artery and from the portal vein. The hepatic veins carry blood to the inferior vena cava, the largest vein in the body, which then carries blood from the abdomen and lower parts of the body to the right side of the heart.

**QUESTION 2:**

The liver is the largest organ inside your body. It helps your body digest food, store energy, and remove poisons.

There are many kinds of liver diseases:

1. Diseases caused by viruses, such as hepatitis A, hepatitis B, and hepatitis C
2. Diseases caused by drugs, poisons, or too much alcohol. Examples include fatty liver disease and cirrhosis.
3. Liver cancer
4. Inherited diseases, such as hemochromatosis and Wilson disease

Symptoms of liver disease can vary, but they often include swelling of the abdomen and legs, bruising easily, changes in the colour of your stool and urine, and jaundice, or yellowing of the skin and eyes. Sometimes there are no symptoms. Tests such as imaging tests and liver function tests can check for liver damage and help to diagnose liver diseases.

1. **Hepatitis**

Hepatitis is a disease caused by inflammation of the liver. It usually results from exposure to a virus, but there are also non-viral forms of the disease, including hepatitis brought on by the use of certain drugs, alcohol abuse, and autoimmune disease. Hepatitis can be acute (lasting just a few weeks to a few months), cause few if any symptoms, and resolve on its own. It can also be chronic, meaning inflammation persists for six months or longer and can lead to serious and even life-threatening complications.

Treatment for hepatitis varies depending on the cause, symptoms, and severity of the disease. It's important to note that there are effective vaccines for two of the viral forms: hepatitis A and hepatitis B.

**Hepatitis Symptoms**

Many people who have hepatitis do not develop symptoms, or they at least do not have symptoms that suggest they have liver disease. When symptoms do develop, it's usually only when hepatitis is chronic and has begun to do damage to the liver.

When caused by a virus, early symptoms of hepatitis often resemble the flu and include:

* Fever
* Headache
* Joint pain
* Nausea

As it progresses or becomes chronic, hepatitis can bring on more distinct symptoms, including (but not limited to):

* Jaundice (yellowing of the skin and whites of the eyes)
* Darkened urine (choluria)
* Clay-coloured stools
* Abdominal pain or discomfort (typically in the right upper quadrant beneath the ribs)

These symptoms usually are self-limiting, although recovery tends to take around a month or so. In the case of hepatitis B, it can take a full four months for symptoms to fully resolve.

Progressive inflammation of the liver can have severe and even life-threatening repercussions. A few examples of complications of chronic hepatitis include a build-up of scar tissue on the liver (severe fibrosis), cirrhosis, liver cancer, and liver failure.

**Causes**

The causes of hepatitis are diverse, ranging from viral infections to genetic disorders and excessive alcohol use. The three most common causes can be broadly categorized as infectious, metabolic, and autoimmune.

Infectious

Viral hepatitis is the most common form of hepatitis worldwide. There are five distinct viruses that can cause hepatitis.

* Hepatitis A virus (HAV)
* Hepatitis B virus (HBV)
* Hepatitis C virus (HCV)
* Hepatitis D virus (HDV)\*
* Hepatitis E virus (HEV)\*

Besides viruses, liver inflammation can be caused by bacteria such as Salmonella and E. coli, as well as parasites that directly attack the liver.

**Diagnosis**

Hepatitis that is asymptomatic often goes undiagnosed. However, certain tell-tale signs, such as jaundice, may prompt a doctor to perform certain blood tests. These include:

Liver enzyme tests that can detect the presence of enzymes that can "escape" into the bloodstream because a damaged liver isn't functioning as it should to prevent this from happening

Antibody tests that look for substances produced by the immune system in response to certain viruses—specifically HAV, HBV, and HCV

Direct viral measures, in which the exact amount of HBV or HCV are evaluated.

More advanced tests for hepatitis may be necessary in some cases, such as ultrasound, computerized axial tomography (CT) scans, or magnetic resonance imaging (MRI).

Sometimes a liver biopsy is necessary to definitively diagnose hepatitis.

1. **Hepatitis B**

Of the adults who get the Hepatitis B virus, 95% clear the virus and do not go on to have the chronic form of the disease. Some people have few symptoms or none at all, so many do not realize they have HBV or that they have had it.

Many adults will clear the virus completely within six months. The good news is that the protective antibodies produced while fighting the infection mean that people who have had it will never have to worry about HBV again—they will be immune.

There are three types of hepatitis B infections:

1. **Healthy chronic carriers of hepatitis B**are not infectious to others and, although they may have a slightly higher risk of cirrhosis and liver cancer than the general population, they mostly live normal lives. The virus can become reactivated if their immune systems become suppressed, such as during a severe illness, during treatment with immunosuppressant drugs for diseases like cancer or AIDS, or with drugs such as steroids.
2. **Chronic infectious hepatitis B** is highly infectious. The person with it may have a very inflamed and damaged liver even when the person has few or no symptoms. People with this type of hepatitis B are more likely to have a progressive disease leading to cirrhosis. Only 5% to 10% have spontaneous remission, become non-infectious to others, and sustain no further or minimal liver damage, although sometimes reactivation of the virus occurs.
3. **Chronic mutant hepatitis B**is a mutated strain of the virus with a permanent alteration of the hepatitis B virus’s genetic makeup. Those with it have the potential to be infectious to others and it is thought to be more resistant to treatment than other forms of the disease.

**Transmission**

Hepatitis B is transmitted through contaminated bodily fluids like:

* Blood
* Sweat
* Tears
* Saliva
* Semen
* Vaginal secretions
* Menstrual blood
* Breast milk

Transmission can also occur when using the same syringe as an infected person, like receiving blood transfusions prior to 1975 (blood supplies are now screened in most countries) and getting tattoos or body piercing.

Hepatitis B can also be transmitted during childbirth from mother to child, during medical procedures, through occupational exposure, and during sexual intercourse. Having Hepatitis B does not necessarily mean that a person is infectious to other people, only some people with HBV are contagious.

**Signs and Symptoms**

There are many ways people may discover they have hepatitis. Because there are sometimes so few specific symptoms beyond fatigue, for example, that it may only be diagnosed when blood tests are performed—sometimes for unrelated reasons, such as prior to giving blood donations, for insurance purposes, for general health checks, or when following work-related injuries.

**Acute Hepatitis B**

In its severe form, hepatitis B symptoms can make the person feel extremely ill. Others may believe they have the flu while some may experience no symptoms at all.

Symptoms include jaundice, fever, abdominal pain, poor appetite, nausea, vomiting, fatigue, dark coloured urine, light-coloured stools, muscle and joint pain, and rash. The liver may also be enlarged and tender.

Fulminant hepatitis is a severe but very rare form of acute hepatitis. It may begin with fatigue and nausea, but, within a few weeks, the signs and symptoms become pronounced. About two weeks after jaundice develops, encephalopathy develops.

Encephalopathy is a state of impaired or altered mental status resulting from the inability of the damaged liver to remove toxins from the blood. In its mild form, there may be some short-term memory loss, forgetfulness, slurring of speech, small behavioural personality or behavioural changes, or changes in sleep patterns.

In its severe form, a person may experience severe loss of memory (not knowing the date, the year, their own name or address), confusion, exhibit inappropriate behaviour, poor coordination, asterixis (uncontrollable flapping of the hands), fetor hepaticus (foul-smelling breath), and coma. Up to 85% of people with this type of rare hepatitis will die without a liver transplant.

**Chronic Hepatitis B**

Again, signs and symptoms can vary and many people will be unaware that anything profound is wrong or experience only vague symptoms. These can include mild or restless fatigue, jaundice, and an enlarged liver. Unfortunately, if chronic hepatitis is not cleared by the body or is not successfully treated and cured, liver disease or liver failure may result.

1. **Hepatitis C (HCV)**

Hepatitis C is an infectious disease of the liver caused by the hepatitis C virus (HCV). It is typically spread through contact with infected blood and can also be transmitted through sexual contact or passed from mother to child during pregnancy.

It is a slowly progressive disease that can range in severity from a mild, flu-like illness lasting a few weeks to a serious, life-long condition that can severely damage the liver, causing inflammation and tissue scarring.

**Hepatitis C Symptoms**

The course of an HCV infection is highly unpredictable. The virus can spontaneously clear in some people, become a persistent infection in others, and advance to a life-threatening illness in others.

The stages of infection are also highly variable and are typically defined as being either acute, chronic, or end-stage, each with its own symptoms.

**Incubation Period:** Most people do not experience their first symptoms of hepatitis until about two to twelve weeks after exposure to the virus, or even longer.﻿ Symptoms of acute hepatitis can take as long as five to six months to appear.

Some people do not go on to experience any symptoms, as the body's immune system may fight off the virus. In as many as one in five cases, the virus will spontaneously clear soon after infection, showing no detectable signs in the blood.

**Acute Hepatitis**: Months after HCV exposure, only a handful of individuals experience mild, flu-like symptoms of hepatitis. Acute hepatitis infection is characterized by the rapid onset of symptoms, if they occur.

Symptoms include:

* Tiredness
* Joint and muscle pain
* Loss of appetite
* Nausea
* Abdominal pain
* Jaundice, which is a yellow colouring of the skin and eyes, may occur as well. A few days before jaundice becomes apparent, some people notice dark-coloured urine or clay-coloured stools.

During an acute infection, HCV primarily targets liver cells called hepatocytes*.*As the virus rapidly replicates—generating upwards of a trillion copies of itself per day—it can cause damage to the liver by directly killing hepatocytes and by stimulating the immune system to produce disease-fighting cells called lymphocytes, which kill the infected liver cells and also cause inflammation of the liver.

**Chronic Hepatitis:** HCV spontaneously improves within six months in about 20 to 25 percent of people with acute hepatitis. When the symptoms do not improve, HCV infection progresses to chronic hepatitis.

For people who develop chronic hepatitis C, the most common complaints are:

* Fatigue
* Loss of appetite
* Nausea
* Weakness
* Weight loss
* Jaundice
* Swelling of the abdomen
* Abdominal pain
* Bruising or bleeding

**End-stage hepatitis C:** In 10 to 20 percent of cases, HCV infection can advance to a condition called cirrhosis in which the liver is so extensively damaged that its ability to function properly is reduced.﻿ This can progress to a stage called decompensated cirrhosis in which the liver is essentially non-functional.

Symptoms of decompensated cirrhosis include:

* Severe weakness and fatigue
* Weight loss
* Abdominal pain
* Itching
* Bruising and bleeding
* Jaundice
* Abdominal swelling
* Memory or behavioural changes
* Trouble walking

Hepatocellular carcinoma, a type of liver cancer, is also commonly seen in advanced cases of hepatitis C, with rates running as high as 17 times that of the general population.

End-stage disease is defined as the stage of disease where the risk of mortality is increased due to liver failure, liver cancer, or non-liver-related complications such as kidney failure. Decompensated cirrhosis and hepatocellular carcinoma are the two most common end-stage conditions associated with HCV infection. Outcomes for both are generally poor, carrying a five-year survival rate of 50 percent and 30 percent, respectively.

**Causes**

HCV is caused by infection hepatitis C virus, which targets the liver. You can become infected with the virus by coming into contact with contaminated blood or through sexual contact.

**Transmission of HCV:** In the United States, HCV is the most common blood-borne infection, impacting around 3.2 million Americans, or roughly 1.5 percent of the adult population.

You can get the virus in the following ways:

* Injecting drug use - about 80 percent of cases
* Sexual contact - about 10 percent of cases
* Mother-to-child transmission - about 4 percent of cases
* Needlestick injury- about 2 percent of cases
* Blood transfusion- less than .01 percent of new cases.

Roughly three in four Americans living with HCV today who were born between 1945 and 1965 became infected due to contaminated blood transfusions.

1. **Liver Cancer**

Liver cancer arises in the liver, an organ located beneath your lower ribs on the right side of your abdomen.﻿ It's important to distinguish primary liver cancer (hepatocellular carcinoma) and bile duct cancer (cholangiocarcinoma) from tumors which begin in other places of the body and spread to the liver (liver metastases). Liver metastases are much more common than primary liver cancers and are treated in the way that a primary cancer (such as lung cancer or breast cancer) are treated, instead of the way that primary liver cancer is treated.

The functions of the liver are important to know as you look at the possible symptoms of the disease. The liver plays roles in detoxifying substances, secreting bile to aid in digestion and making hormones that are important in the production of red blood cells.

﻿ In addition to the cancers mentioned above, there are less common types of liver cancer. A few of these include hepatoblastoma, a rare form of childhood cancer, and angiosarcoma of the liver. This review will focus primarily on primary liver cancer and bile duct cancer.

**Liver Cancer Symptoms**

Liver cancer symptoms are uncommon in the early stages of the disease unless the tumor lies near one of the bile ducts and causes an obstruction (with symptoms similar to a gallbladder attack).﻿ Early stages include stage 1, where the tumor hasn't yet spread. In stage 2 liver cancer, several small tumors may be present and may spread to nearby blood vessels. As the tumor spreads to nearby organs it becomes categorized as stage 3 liver cancer. Stage 4 means that the cancer has spread to distant organs and sites, such as the lungs, bones, and adrenal glands.

Generally, symptoms may include:

* Pain in the right upper abdomen
* A mass in the right abdomen (just under your ribs or potentially lower)
* Right shoulder blade pain
* Jaundice, a yellowish discoloration of the skin and the whites of the eyes
* Pale or white stool
* Dark urine
* Intense itching
* Ascites, the build-up fluid in the abdomen
* Fever (101 degrees or higher that lasts for several days without obvious signs of infection)
* Unintentional weight loss without a significant change in diet or exercise
* Nonspecific symptoms such as loss of appetite, fatigue, and a general sense of being unwell

**Causes**

We aren't certain exactly what causes the disease, though we know of several risk factors for liver cancer. Most of these risk factors result in scarring (cirrhosis) of the liver, though liver cancer may also develop without cirrhosis.

The most common risk factor for liver cancer is one of the forms of hepatitis. Together, **hepatitis B and hepatitis C** are thought to be the cause of over half of liver cancers worldwide.﻿ Some of the risk factors include:

* **Alcohol use and smoking:**Long-term heavy alcohol use (more than 3 drinks per day) is clearly associated with the development of cirrhosis, and can also raise the risk of liver cancer. Smoking also appears to raise the risk, especially when combined with other risk factors, such as hepatitis B.
* **Family history and genetic diseases:**If you have a family member who has liver cancer, your risk is higher than average. The risk is also increased for those who have genetic diseases such as hemochromatosis and Wilson's disease.
* **Medical conditions:**Medical conditions that increase the risk of liver cancer include primary sclerosing cholangitis, primary biliary cirrhosis, non-alcoholic fatty liver disease, and diabetes.
* **Aflatoxin exposure:**Uncommon in the United States, but common worldwide, exposure to aflatoxins—toxins released by fungi that grow on improperly stored grains and nuts—is a significant cause of liver cancer.

**Diagnosis**

Those who have any symptoms of liver cancer or risk factors for developing the disease should see their doctor.﻿ A physician can take a careful history and perform a physical exam. For some, screening tests may be considered. Depending on the evaluation, a combination of blood tests and imaging studies may also be done to form a diagnosis.

* **Labs and tests:**Blood work (such as liver function tests), a hepatitis panel, and tumor markers are often the first steps in diagnosing liver cancer.﻿ One specific test, the alpha-fetoprotein tumor marker test (AFP), may be ordered to screen for liver diseases.
* **Imaging:**The first imaging test that is usually done is an ultrasound.﻿ Other tests that may be helpful in diagnosis include MRI and CT scans. An angiogram of the liver may also be recommended.
* **Biopsy:**Unlike many cancers, the diagnosis of liver cancer is often made based on imaging findings rather than biopsy. A biopsy may not be needed unless it is important to understand the molecular characteristics of the tumor, such as in a clinical trial.

1. **Cirrhosis**

Cirrhosis is the extensive scarring (fibrosis) of the liver caused by long-term injury. The damage is due to persistent and ongoing inflammation in response to chronic liver injury, whether from chronic viral hepatitis infection, excessive alcohol consumption, or a variety of other causes.

The liver has the ability to repair itself. However, as it gradually builds up scar tissue, it is less able to function properly. Over time, as the amount of scarring increases and the circulatory flow to the liver is decreased, essential liver functions are compromised. In some cases, this can lead to liver failure and even death. Over one million people die each year of cirrhosis. Cirrhosis is now the 9th leading cause of death in the Unites States, affecting nearly twice as many men as it does women.

**Cirrhosis Symptoms**

The progression of liver damage from early-stage fibrosis to cirrhosis generally takes years, and even decades, to manifest symptomatically. In the early years, there are often few, if any, symptoms.

When symptoms do appear, they are sometimes misdiagnosed, ignored, or attributed to other possible causes.﻿ As the disease progresses, however, the tell-tale symptoms can become more apparent. These symptoms include:

* Fatigue
* Confusion
* Weakness
* Itching
* Loss of appetite
* Weight loss
* Nausea
* Easy bruising
* Jaundice (the yellowing of skin and/or eyes)
* Spider angioma (the spider veining on the skin, often around the nose and cheeks)
* Edema (the swelling of feet, ankles, and legs due to a buildup of fluid)
* Abdominal bloating from ascites (a buildup of fluid in the belly)﻿

Many of these symptoms are caused by portal hypertension, in which scar tissue partially blocks the normal flow of blood to the liver.

**Causes**

The most common causes of cirrhosis are alcohol-related liver disease, hepatitis B, hepatitis C, and non-alcoholic fatty liver disease.

* **Alcohol-related liver disease** follows close behind and is typically associated with heavy drinking over several years (on average, over two drinks per day for women and over three for men ten or more years).
* **Hepatitis B**-related cirrhosis is a prevalent cause of cirrhosis.﻿ Vaccination against hepatitis B in many countries has been successful in decreasing the rates of hepatitis B-related complications, like cirrhosis and liver cancer.
* **Hepatitis C** is one of the greatest causes of cirrhosis diagnoses in the United States, as well as being the leading indicator for liver transplants.
* **Non-alcoholic fatty liver disease** is typically associated with obesity, as well as diabetes, high blood pressure, and high cholesterol. People with metabolic syndrome, characterized by large waist sizes, high triglycerides, abnormal cholesterol level, high blood pressure, and higher than normal blood glucose levels, are most prone to cirrhosis.

Some less common causes of cirrhosis are obstructed bile ducts of the liver and gallbladder, autoimmune hepatitis, and hereditary diseases like Wilson's disease or hemochromatosis, medication and celiac disease.

**Diagnosis**

Liver biopsy is the most accurate way to diagnose cirrhosis and to properly assess the stage of the liver disease. An ultrasound or magnetic resonance elastography are non-invasive ways to detect liver fibrosis. A number of blood tests and imaging tools (including ultrasound, CT scan and, MRI) can be used to monitor disease progression.

Cirrhosis can be typically classified as either compensated or decompensated. Compensated cirrhosis is simply a damaged liver that is still relatively functional, while decompensated cirrhosis represents acute deterioration of liver function. If complications cannot be controlled when the liver ceases functioning, liver transplantation is typically indicated.

About 5 percent of people with cirrhosis will develop hepatocellular carcinoma (HCC), the most common form of liver cancer.

**Treatment**

Many cases of cirrhosis are manageable for many years before they progress and require transplantation. Management of cirrhosis is largely dependent on the cause and severity of the disease, but it should start as soon as it is diagnosed.

Cirrhosis is generally not curable except by liver transplantation.

Iron overload is an excess storage of iron in the body. It can occur for a few different reasons. Primary iron overload is caused by hemochromatosis, an inherited condition. But it may also develop secondary to multiple blood transfusions, which may be needed by those with types of blood cancer. Iron overload can damage the heart, liver, and other organs if untreated.

**Symptoms**

In 75% of the cases, a person with iron overload will have no symptoms, although feelings of fatigue may begin early in the course of the condition.﻿

However, once iron has built up in various organs, you may begin to experience more prominent symptoms. These can include:

* Joint pain (when in the knuckles, this is called "iron fist")
* Abdominal pain
* Loss of sex drive
* Skin colored grey or bronze

Untreated, the accumulation of iron can lead to:

* Heart failure
* Infertility
* Diabetes
* Cirrhosis of the liver
* Arthritis
* Hypothyroidism (under-active thyroid)
* Impaired growth
* Erectile dysfunction
* Cancer
* Depression

Some evidence also suggests bacterial infection may be one of the consequences of iron overload, as iron build-up in the white blood cells impairs their ability to fight invading organisms.﻿

**Causes**

Iron has a very important role in your body. It plays a part in many biological processes, including the synthesis of DNA when cells divide and the transportation of oxygen from the lungs to cells and tissues.

Iron that you take in through food generally binds to a protein called transferrin and circulates around in your blood plasma. For the most part, this iron is used to form hemoglobin, the substance in red blood cells that transports the oxygen you breathe into your tissues. Leftover iron is stored in the liver for future use.

The human body does not have the ability to purposefully remove or excrete excess iron, although some iron is lost in normal processes such as the shedding of skin cells.﻿ Once the body’s maximum iron storage capacity is reached, iron begins to build up in other parts of the body, leading to iron overload.

When iron has overwhelmed the body’s ability to safely store it, it can cause harm in a number of ways:

* When there is more iron in the body than transferrin for it to bind to, it circulates around by itself as **non-transferrin-bound iron (NTBI)**. This form of iron is toxic to the body and causes damage to tissues and organs at a cellular level.
* Excessive iron accumulates in the heart, lungs, brain, endocrine glands, liver, and even the bone marrow.