Understanding Blood Tests

Blood tests (blood panels), are used to determine physiological and biochemical states, such as disease, electrolyte content, drug effectiveness, and how various organs (e.g., kidneys and liver) are functioning. Blood can be analyzed for a number of different tests. We will focus on the most common including an arterial blood gas (ABG), chemistry panel (screen), complete blood count (CBC), and a lipid profile. Here is a brief explanation of the abbreviations used in measurements followed by descriptions of several common test components.

Units Used for Blood Test Measurements

Blood tests use the metric measurement system and abbreviations such as the following:

- cmm: cells per cubic millimeter
- g/dL: grams per deciliter
- IU/L: international units per liter
- mEq/L: milliequivalent per liter
- mg/dL: milligrams per deciliter
- mL: milliliter
- mmol/L: millimoles per liter
- ng/mL: nanograms per milliliter
- pg (picograms): one-trillionth of a gram

Chemistry Panel or Screen (Metabolic Panel)

The most complete form of a chemistry screen (called a chem-20, SMA-20, or SMAC-20 - Sequential multi-channel analysis with computer-20) looks at 20 different components in the blood. Other types of chemistry screens (such as an SMA-6, SMA-7, or SMA-12) look at fewer.

Normal Values

- Albumin: 3.9 to 5.0 g/dL
- Alkaline phosphatase: 44 to 147 IU/L
- ALT (alanine transaminase): 8 to 37 IU/L
- AST (aspartate aminotransferase): 10 to 34 IU/L
- BUN (blood urea nitrogen): 7 to 20 mg/dL
- Calcium - serum: 8.5 to 10.9 mg/dL
- Serum chloride: 101 to 111 mmol/L
- CO2 (carbon dioxide): 20 to 29 mmol/L
- Creatinine: 0.8 to 1.4 mg/dL **
- Direct bilirubin: 0.0 to 0.3 mg/dL
- Gamma-GT (gamma-glutamyl transpeptidase): 0 to 51 IU/L
- Glucose test: 70 to 100 mg/dL
- LDH (lactate dehydrogenase): 105 to 333 IU/L
- Phosphorus - serum: 2.4 to 4.1 mg/dL
- Potassium test: 3.7 to 5.2 mEq/L
- Serum sodium: 136 to 144 mEq/L
- Total bilirubin: 0.2 to 1.9 mg/dL
- Total cholesterol: 100 to 240 mg/dL
- Total protein: 6.3 to 7.9 g/dL
- Uric acid: 4.1 to 8.8 mg/dL

Note: Normal value ranges may vary among different laboratories.
**Glucose Test.** Also called a blood sugar test

**Reason for Test:**

The blood glucose test is typically used to:

- Screen for both **high blood glucose** (hyperglycemia) and **low blood glucose** (hypoglycemia) levels
- Diagnose **diabetes mellitus.** Diabetes mellitus is a group of metabolic diseases characterized by hyperglycemia resulting from defects in either insulin secretion (Type I) or insulin action (Type II, Type III and Gestational Diabetes). Gestational Diabetes can occur during pregnancy.
- Monitor glucose levels in persons with diabetes mellitus

**Physiological Function:** Glucose is a monosaccharide or simple sugar. The primary function of glucose is to provide energy for physiological processes such as respiration and muscle contraction. **The brain primarily uses glucose for energy** and to a minor extent, the breakdown products of fat. **Insulin plays a minor role in the uptake or use of glucose in brain cells (neurons).** Glucose moves into the neurons by **facilitated diffusion** primarily through special glucose transporters known as **glucose transporter number 3 (GLUT 3).** These transporters are not regulated by insulin and are always present. To move glucose into the neuron the glucose concentration outside the neuron needs to remain higher so glucose continually diffuses in. Therefore, it is essential that the blood glucose level always be maintained within the normal range, which is one of the most important functions of the blood glucose control system – keep the brain properly fueled.

When blood glucose falls too low, into the range of **20 to 50 mg/dL,** symptoms of **hypoglycemic shock** develop, characterized by progressive nervous irritability, shaking, and sweating that if untreated, could lead to fainting, seizures, and coma. Humans are well adapted to periodic eating and fluctuations in blood glucose levels. We are able to gain weight when food is plentiful and when food is unavailable, continue our normal bodily functions for long periods of time (hours to weeks). Carbohydrates can be converted to **glucose, which is stored as glycogen** in the liver and skeletal muscle. **Proteins** are not stored in the classical sense but can be used to make muscle as contractile proteins and broken down later to supply energy. **Fat** can be stored in adipose tissue. Two hormones (glucagon and insulin) produced by the pancreas play a major role in regulating which fuels are used and how they are released from storage.
**Glucagon:** Glucagon generally (exception is gluconeogenesis) promotes **catabolic reactions** during times of decreased food availability (fasting). When **blood glucose** levels **decrease** below the normal fasting range (70-100 mg/dL) glucagon is produced by α cells (alpha cells) within the islets of Langerhans of the pancreas. **Glucagon has three major functions:** 1) Increases blood glucose levels by the breakdown of liver glycogen (glycogenolysis), 2) Increases gluconeogenesis in the liver and 3) Stimulates the breakdown of fat.

1) **Glucagon increases blood glucose levels by the breakdown of liver glycogen (glycogenolysis).** Glucagon travels through the blood to the liver where it stimulates hepatocytes to breakdown glycogen into glucose – process called **glycogenolysis.** The glucose is released and increases blood glucose levels to reestablish homeostasis.

2) **Glucagon stimulates gluconeogenesis in the liver.** Gluconeogenesis is the metabolic process that results in the generation of glucose from non-carbohydrate substrates such as pyruvate, lactate, glycerol, and amino acids. There are only about **100 grams** of stored glycogen in the liver, so adequate blood glucose levels could not be maintained for very long during fasting using only this source. Glucagon increases the rate of **gluconeogenesis and the glucose made** can either be stored as glycogen or released into the blood and increase blood glucose levels. **Note:** Although glucagon increases amino acid uptake into the liver cells **glucagon does not cause a breakdown of muscle protein.** Decreased insulin levels can stimulate protein breakdown in **skeletal muscle** which provides amino acids for the conversion to glucose by the liver.

3) **Glucagon stimulates the breakdown of fat.** In adipose cells glucagon activates the enzyme lipase to **breakdown triglycerides and release free fatty acids and glycerol into the blood.** The liver converts some of these fatty acids into ketone bodies and uses the glycerol to make glucose. Several organs use fatty acids and ketone bodies as an energy source.

**Note:** The release of glucose from the liver during fasting helps **provide the brain with the glucose** it needs. Because insulin secretion is low during fasting, skeletal muscles cannot utilize blood glucose as an energy source. Instead, **skeletal muscles** – as well as the **heart, liver and kidneys** – use free
fatty acids and ketone bodies as their major source of fuel. This helps to “spare” glucose for the brain.

**Insulin:** Insulin promotes anabolic reactions during times of increased food absorption. Insulin has three major functions: 1) decreases blood glucose levels by increasing glucose uptake into cells and stimulates glycogen formation, 2) promotes fat production and storage, and 3) stimulates the uptake of amino acids and production of proteins.

1) **Insulin lowers blood glucose levels by increasing glucose uptake into cells and stimulates glycogen formation:** When blood glucose levels rise above normal fasting range (70-100 mg/dL) the hormone insulin is produced by β cells (beta cells) within the islets of Langerhans of the pancreas. Insulin lowers blood glucose levels by stimulating the uptake of glucose by cells and promotes the conversion of glucose into glycogen (glycogenesis). Glycogen formation is especially important in skeletal muscle and liver cells. Insulin binds to its receptors and stimulates the insertion of GLUT 4 transporter channels into the plasma membrane (due to the fusion of intracellular vesicles with the plasma membrane). Glucose transporters (GLUTs) are integral membrane proteins that transport glucose and other hexoses such as fructose and galactose into the cell by facilitated diffusion. Currently there are 12 GLUT protein transporters known but we will focus on GLUT4 because its insertion into the membrane is regulated by insulin – it is an insulin-regulated glucose transporter. GLUT 4 is primarily found in adipose tissues, skeletal muscle, and cardiac muscle.

2) **Insulin promotes fat synthesis and storage.** Once the stores of liver and muscle glycogen have been filled, insulin stimulates the liver to use the additional glucose to synthesize fatty acids. The fatty acids are transported in lipoproteins from the liver to adipocytes to be stored as fat. Insulin also facilitates entry of glucose into adipocytes, and within those cells, glucose can be used to synthesize glycerol. This glycerol, along with the fatty acids delivered from the liver, is used to synthesize triglycerides within the adipocyte. By these mechanisms, insulin is involved in further accumulation of triglyceride in fat cells.

3) **Insulin stimulates the cellular uptake of amino acids and their incorporation into proteins.** High blood levels of amino acids along with glucose, stimulates the secretion of greater amounts of insulin. Amino acids administered in the absence elevated levels of glucose cause only a small
increase in insulin secretion. **Note:** Decreased insulin levels can cause protein breakdown in skeletal muscle which provide amino acids for the conversion to glucose by the liver.

**Glucose Testing**

Depending on the purpose of testing, glucose may be measured on a **fasting** basis (collected after an 8- to 10-hour fast), **post prandial** (after a meal), **random** (anytime), and/or as part of a **oral glucose tolerance test** (OGTT / GTT).

**Fasting blood glucose (FBG) levels** has a normal range of 70 to 100 milligrams per deciliter (mg/dL). **Note:** 100 mL = 1 dL. In a normal individual after eating, blood glucose levels generally do not get above 140 mg/dL. Thus, **Non-fasting normal blood glucose level ranges between 70 to 140 mg/dL** and is dependent on when the person last ate. In **diabetic mellitus** patients, we see both low blood glucose levels (**hypoglycemia**), and elevated blood sugars (**hyperglycemia**). When the blood glucose drops to about 60 mg/dL, a person will generally have symptoms of shakiness, feeling of hunger, nausea, anxiety, irritability, increase sweating and heart rate. If blood sugar drops between 20 and 50 mg/dL, then there is a **progressive loss of mental function**, confusion, and eventually unconsciousness, seizures, and coma. On the other side, if blood glucose gets up above 180 to 200 mg/dL, then it exceeds the capacity of the kidneys to reabsorb the glucose and will begin to spill glucose into the **urine**. If is rises above 400 mg/dL it can cause alteration in mental function. **There can be impaired mental function with either too low or exceedingly high blood glucose.**

**The hemoglobin A1c test** (HbA1c) or glycated hemoglobin test. **Hemoglobin A1c provides an average of a person’s blood sugar over the past 3 months.** It measures what percentage of your hemoglobin is coated with sugar (glycated). Test is used to diagnose diabetes mellitus and in conjunction with daily blood glucose monitoring to make adjustments in a person’s diabetes medicines.

**Hemoglobin** is an oxygen-transport protein found inside red blood cells (RBCs). There are several types of normal hemoglobin, but the predominant form – about 95-98% – is **hemoglobin A** which consists of **two alpha chains and two beta chains**. As glucose circulates in the blood, some of it spontaneously binds to hemoglobin A. The hemoglobin molecules with attached glucose are called **glycated hemoglobin**. The higher the concentration of glucose in the blood, the more glycated hemoglobin is formed. Once the glucose binds to the hemoglobin, it remains there for the **life of the red blood cell** – normally about 4 months (120 days). **Glycated Hemoglobin is normal** at low amounts; however when blood glucose levels are abnormally high as in the case of uncontrolled diabetes mellitus, high amounts of blood glucose combines with hemoglobin. **Therefore, the average amount of sugar in your blood can be determined by measuring a hemoglobin A1c level.** If your glucose levels have been high over recent weeks, your hemoglobin A1c test will be higher.

**Hemoglobin A1c Test Results:** For people without diabetes, the normal range for the hemoglobin A1c test is between 4% and 5.6%. So if you have a 5% A1C, it means that 5% of your
hemoglobin proteins are glycated. Hemoglobin A1c levels between 5.7% and 6.4% indicate increased risk of diabetes, and levels of 6.5% or higher indicate diabetes mellitus. People with diabetes should have this test every three months to determine whether their blood sugars have reached the target level of control. Those who have their diabetes under good control may be able to wait longer between the blood tests, but experts recommend checking at least 2 times a year.

Diabetes Mellitus

- Diabetes mellitus is a group of metabolic disorders characterized by prolonged increase in blood glucose levels (hyperglycemia) resulting from defects in insulin secretion, insulin action, or both. Exception to hyperglycemia is type III diabetes – details discussed later.
  - The chronic hyperglycemia can cause damage to various organs, especially the eyes, kidneys, nerves, heart, and blood vessels.
  - Meaning of the word diabetes mellitus
    - Diabetes means “a passer through; a siphon” used to describe the excessive discharge of urine.
    - Mellitus means “sweet or sweetened with honey” due to the increased glucose in the urine (glucosuria or glycosuria).
- Symptoms for diabetes mellitus: Except for type III, the classic symptoms consist of the three “polys”:
  - Polyuria: Excessive urine production due to high glucose content in kidney filtrate and thus urine, which results in decreased ability to reabsorb water hence large volumes of water are lost in the urine.
  - Polydipsia: Excessive thirst due to large volumes of water lost in the urine resulting in dehydration
  - Polyphagia: Excessive appetite. Even through the person is hyperglycemic, glucose cannot enter the cells. The hypothalamus controls appetite and if glucose cannot enter the cells of the hypothalamus then the person feels extremely hungry.
- Other symptoms can include blurry vision, headache, fatigue, slow healing of cuts, itchy skin and blurry vision.
  - Prolonged high blood glucose can cause glucose absorption in the lens of the eye, which leads to changes in its shape, resulting in vision changes.

Types of Diabetes: There are four forms of this disorder, Type I, Type II, Type III and gestational diabetes.

- Type I Diabetes or Insulin-Dependent Diabetes Mellitus (IDDM): Deficiency of insulin due to a loss of the insulin-producing beta cells of the islets of Langerhans in the pancreas. Accounts for about 10% of diabetes mellitus cases.
  - Cause: Classified as either an autoimmune disorder or idiopathic (unknown cause). The majority of type 1 diabetes is due to an autoimmune disorder where the immune system attacks the beta cells.
  - Appears to be a genetic link - in genetically susceptible people, the onset of type I diabetes can be triggered by one or more environmental factors, such as a viral infection.
  - Treatment: Insulin injections
If untreated, symptoms are similar to a starving person; Fats and proteins are broken down to provide an energy source for metabolism, results in the wasting away of body tissues. The liver converts some of the breakdown products of fat to ketone bodies. **Ketone bodies** are used for energy by many organs such as the heart and brain and normally found in blood in relatively low concentrations. **Ketone bodies** include acetoacetic acid, β-hydroxybutyric acid, and acetone.

- Elevated levels of ketone bodies in the blood — a condition called **ketosis**.
- If there are sufficient amounts of ketone bodies in the blood to lower the blood pH, the condition is called **ketoacidosis**. Severe ketoacidosis, which may occur in diabetes mellitus, **can lead to coma and death**.
- A person in this condition may also have a sweet-smelling breath due to the presence of acetone, which is volatile and leaves the blood in the exhaled air.

**Type II Diabetes** or Non-Insulin-Dependent Diabetes Mellitus (NIDDM): The cells **insulin receptors** are not responsive (insensitive) to insulin, which may be at normal or elevated levels. Accounts for about 90% of diabetes mellitus cases.

- **Cause:** Due primarily to lifestyle factors and genetics. Lifestyle factors include obesity, lack of physical activity, poor diet, and stress. May go unnoticed for years in a patient before diagnosis, since the symptoms are typically milder and sporadic.
- **Type II** may progress to destruction of the insulin-producing cells due to their overstimulation, but is still considered Type 2, even though insulin administration may be required. Usually controlled and corrected by exercise, proper diet, and weight loss.
- **Treatment** concentrates on keeping blood sugar levels close to normal. This can usually be accomplished with a healthy diet, exercise, weight loss, and use of appropriate medications. With regular exercise, skeletal muscle fibers **up-regulate both the number of GLUT4 glucose transporters and the number of insulin receptors on their membrane.** The addition of **insulin-independent GLUT4 transporters** decrease the muscle’s dependence on insulin for glucose uptake which correct the hyperglycemia of diabetes. The **up-regulation of insulin receptors** with exercise makes the muscle fibers more sensitive to insulin. A small amount of insulin then can achieve a response that previously required more insulin. Because the cells are responding to lower insulin levels the **pancreases secrete less insulin.** This lesson the stress on the pancreas, resulting in a lower incidence of type II diabetes mellitus eventually requiring insulin. **Oral Medications** such as metformin (Glucophage) lowers blood glucose concentrations by suppressing glucose production (gluconeogenesis) in the liver, decreases glucose absorption from the intestines, and increases insulin sensitivity of insulin receptors.

**Type III Diabetes** is a type of Insulin resistant diabetes (discovered in 2005) confined to the brain, characterized by a decrease in brain insulin, insulin receptors, insulin-like growth factors I and II (IGFs), and mitochondrial dysfunctions. In the brain insulin binds to receptors at a synapse and turns on mechanisms necessary for nerve cells to survive and memories to form. Type III diabetes represent a major pathogenic
mechanism of Alzheimer’s disease (AD), which involves brain shrinkage due to cell loss especially in the hippocampus which functions in learning and memory formation. There is the build-up of abnormal clusters of protein outside the neurons called amyloid plaques, and within the neurons are neurofibrillary tangles made up of a protein called tau (TAW) that has been hyperphosphorylated. The neurofibrillary tangles cause microtubules to disintegrate, destroying the structure of the cell’s cytoskeleton which collapses the neuron’s transport system. Post mortem brain studies found that insulin and IGF I and II are reduced in the cortex, hippocampus and hypothalamus.

- **Type II diabetes** and obesity may contribute to the development of AD but by themselves have not shown to cause AD.
- **Type III diabetes** may be treated with insulin (if low levels) and insulin sensitizing agents that can increase insulin receptor expression and enhance the binding to insulin, i.e., drugs currently used to treat type II diabetes as well as regular exercise and a healthy diet.

Diagnosis may be done using functional Magnetic Resonance Imaging (MRI) or Positron Emission Tomography (PET). AD generally starts with deterioration in the hippocampus. The disease then tends to spread from front to back of the cerebral cortex, until reaching the brain stem, where involuntary functions such as breathing, heart rate and blood pressure are regulated.

For more information see review article by Suzanne de la Monte and Jack R. Wands, Alzheimer’s Disease Is Type 3 Diabetes—Evidence Reviewed, 2008.
• **Gestational diabetes** Can occur during pregnancy (especially during third trimester) – women exhibit high blood glucose levels. Occurs in about 5-10% of pregnancies. The cause is thought to be due to **high levels of pregnancy hormones** which cause **insulin receptors to be less sensitive to insulin** and elevate blood sugar levels. Similar to the situation in type II diabetes. Tested by an oral glucose tolerance test (OGTT). **Risks:** Untreated can have increased risk of an **enlarged baby (macrosomia)** at birth which may lead to delivery complications, low blood sugar, and jaundice. Gestational diabetes usually resolves itself after pregnancy. Women with **unmanaged gestational diabetes** are at **increased risk of developing type II diabetes mellitus.**

### Criteria for Diagnosing Diabetes

To be diagnosed with **diabetes mellitus**, you would have at least one of the following criteria as described by the American Diabetes Association (published in Diabetes Care, 2014)

- Have a **hemoglobin A1c** that is 6.5 % or higher.
- Have a **fasting blood sugar level** that is **equal to or greater than 126 mg/dL.** A fasting blood sugar test (fasting plasma glucose) is done after not eating or drinking anything but water for 8 to 10 hours.
- Have a 2-hour **oral glucose tolerance test (OGTT)** result that is equal to or greater than **200 mg/dL.** The glucose drink (load) should contain **75g of glucose** dissolved in water. An OGTT is usually the test done to check for gestational diabetes that occurs with pregnancy (gestational diabetes).
- Have **symptoms of diabetes** (increased thirst, increased urination, increased appetite, and unexplained weight loss) and a blood sugar level equal to or **greater than 200 mg/dL.** The blood sugar test is done at any time, without regard for when you last ate (it’s a random plasma glucose test or random blood sugar test).

To be diagnosed with **prediabetes** (blood sugar is above normal but not high enough to be classified as having diabetes) you have the following:

- Results of your **fasting blood sugar** test are between **100 mg/dL and 125 mg/dL,**
- Have **OGTT** result is between **140 to 199 mg/dL** (2 hours after the beginning of the test),
- Have a **hemoglobin A1c** that is **5.7 to 6.4%**.

If you receive a diagnosis of diabetes, additional blood tests will be run to distinguish between type I and Type II diabetes. Tests will check for detection of a **low C-peptide** and **autoantibodies** that are common in **type I diabetes.** There are four antibody types that can be tested for including islet cell autoantibodies and insulin autoantibodies. The **presence of ketones** — byproducts from the breakdown of fat — in your urine also suggests type I diabetes, rather than type II.
Basis for the insulin and C-Peptide Test:

Insulin is synthesized in the beta cells of the pancreas. Insulin is initially synthesized in the form of proinsulin which consists of three chains of peptides, A, B, and C. Further modification by the Golgi apparatus cleaves portions of the molecule to form insulin, composed of the A and B chain connected by disulfide linkages, and the C chain peptide, called connecting peptide (C-peptide). The secretory vesicle then releases insulin and C-Peptide into the blood. The **insulin tests** measure the amount of insulin in the blood and the **C-peptide test** measures the level of this peptide in the blood. It is generally found in amounts equal to insulin because insulin and C-peptide are linked when first made by the pancreas. Insulin helps the body use and control the amount of sugar (glucose) in the blood. Insulin allows glucose to enter body cells where it is used for energy. The level of C-peptide in the blood can show how much **endogenous insulin** is being made by the pancreas. C-peptide does not affect the blood sugar level in the body. A C-peptide test can be done when diabetes has just been found and it is not clear whether type I diabetes or type II diabetes is present. A person whose pancreas is deficient in insulin production (type I diabetes) will have a low level of blood insulin and C-peptide. A person with type 2 diabetes can have normal or high levels of insulin and C-peptide.

So if an insulin test and C-peptide test both help in determining the amount of blood insulin what is the reason for testing for both? The following are some reasons of C-peptide testing:

1) If a person is treated with insulin injections the C-peptide test will determine how much insulin a person’s pancreas is still producing (**endogenous insulin**).

2) People who are on insulin therapy, regardless of the source of the insulin, may develop **antibodies** to insulin. These typically interfere with tests for insulin, making it nearly impossible to directly evaluate **endogenous insulin production**. In these cases, C-peptide measurement is a useful alternative to testing for insulin.

3) In **type 2 diabetes**, the body is resistant to the effects of insulin (insulin resistance) and it compensates by producing and releasing more insulin, which can also lead to beta cell damage. Type 2 diabetics usually are treated with oral drugs to stimulate their body to make more insulin and/or to cause their cells to be more sensitive to the insulin that is already being made. Eventually, because of the beta cell damage, type 2 diabetics may make very little insulin and require injections. Any insulin that the body does make will be reflected in the C-peptide level; therefore, the C-peptide test can be used to monitor beta cell activity and capability over time and to help a health practitioner determine when to begin insulin treatment.
BUN (blood urea nitrogen) Test

Reason for Test

The blood urea nitrogen test is typically used to:

- Determine if the kidneys are working normally.
- Determine if kidney disease is getting worse.
- Determine if treatment of kidney disease is working.

A blood urea nitrogen (BUN) test measures the amount of nitrogen in the blood that comes from the waste product urea. The test is conducted to see how well your kidneys are functioning. If the kidneys are not able to remove urea from the blood normally, the BUN level rises (a condition called uremia). BUN levels may be elevated in both acute and chronic renal (kidney) failure. Various diseases damage the kidneys and cause problems with urine formation and excretion. Congestive heart failure leads to a low blood pressure and consequent reduced filtration rates through the kidneys, therefore, BUN may be elevated. A diet high in protein can also make the BUN level higher. Liver disease or damage can lower your BUN level because most of the urea is produced in the liver.

Physiological Function: Urea comes from the breakdown of proteins – specifically the amino acids that are the building blocks of proteins. Excess proteins/amino acids cannot be stored by the body and if not needed at that time, they are broken down for energy or converted to fat. Deamination is the process in which an amino group is removed from an amino acid. The process happens in the liver and to a lesser extent in the kidneys. The amino (NH₂) group that is removed becomes a molecule of ammonia (NH₃). The rest of the amino acid that is made up of mostly carbon and hydrogen, becomes a molecule known as a keto acid (ex: Krebs cycle intermediates). Ammonia is very toxic and most of the ammonia is converted by liver cells to less toxic urea which is released into the blood and excreted by the kidneys into the urine. A small amount of urea is also secreted in perspiration. During the process known as the urea cycle, 2 ammonia molecules are added to a carbon dioxide molecule to form urea (NH₂)₂CO. The
Keto acid may be oxidized via the citric acid cycle as a source of energy or converted to glucose via gluconeogenesis or fat via lipogenesis. Ammonia is also produced by the catabolism of amino acids in peripheral tissues, especially skeletal muscle. Since only the liver and kidneys can convert ammonia into urea the other tissues must convert ammonia into a less toxic compound to transport it to the liver where it will be converted to urea.

Gastrointestinal microorganisms convert dietary amino acids into ammonia in the gastrointestinal system. A good portion of this ammonia is absorbed through the intestine and into the portal circulation, taken up by the liver and converted in the liver, via the urea cycle, into urea. Urea is then excreted into the gastrointestinal system and into the urine.
Liver Function Tests
The liver filters and processes blood as it circulates through the body. It metabolizes nutrients, detoxifies harmful substances, makes blood clotting proteins, and performs many other vital functions. Liver function tests are groups of clinical blood tests designed to give information about the state of a patient's liver. The main parameters measured include albumin, bilirubin, and prothrombin time (PT).

Albumin
The liver makes albumin, an essential protein that circulates in blood. Albumin levels are low in people with severe chronic liver disease or malnourishment, because the liver is not able to make the normal amounts of albumin. However, albumin levels may fall in a variety of medical conditions.

Physiological Function: Albumin is the most abundant protein in blood plasma (~ 60%) and functions to maintain osmotic pressure of the vascular system and serve as a carrier protein for hydrophobic substances such as steroid hormones, fatty acids, phospholipids, and biliruben. At the capillaries materials are exchanged with the surrounding tissue. Capillary pressure at the beginning of the capillary (arteriole end) forces fluid and dissolved substances through the capillary pores into the interstitial spaces. Towards the end of the capillary (venule end), the osmotic pressure that results from the plasma proteins (called colloid osmotic pressure), causes fluid to move by osmosis from the interstitial spaces into the blood, thus preventing a significant loss of fluid volume. The excess fluid that is not returned to the capillaries is returned to circulation by the lymphatic system.

The colloid osmotic pressure is influenced by proteins – primarily albumin. This is due to the fact that proteins do not diffuse readily through the capillary membrane. Therefore, the concentration of protein in plasma is 2 to 3 times greater than proteins found in the interstitial fluid. When there is a significant decrease in albumins, edema can result because a greater portion of fluid remains within the interstitial space instead of returning back to the vasculature.
Bilirubin

This test measures the amount of bilirubin in the blood in order to evaluate liver function. Bilirubin levels may be elevated in people with severe liver disease, gallbladder disease, or other bile system conditions that impair bile flow. Increased bilirubin levels can also result from internal hemorrhage and certain hemolytic anemias (increased destruction of RBCs) such as sickle cell anemia or transfusion reactions. High bilirubin levels cause jaundice, in which the skin and whites of the eyes turn yellow.

Physiological Functions: Bilirubin is a waste product from the breakdown of red blood cells (RBCs). Red blood cells have a lifespan of ~120 days. Old and damaged RBCs are engulfed by macrophages in the spleen, liver, and bone marrow and broken down. The hemoglobin is disassembled into heme and globin portions. The globin proteins are broken down into amino acids for reuse. Heme units are stripped of their iron and the iron is reused in erythropoiesis. The remainder of the heme is converted into a pigment called biliverdin (green color) and then to bilirubin (yellow color). Most of the bilirubin is excreted by the liver into the bile and the remainder by the kidneys. The liver processes bilirubin so it can be excreted in the bile and eliminated in the stool. Bilirubin flows through the liver’s bile ducts, dissolved in bile. Bilirubin and its derivatives such as urobilins, give urine its characteristic yellow color. Inside the large intestine, bacterial convert the bilirubin into other forms that give feces its characteristic brown color. Thus, white or clay colored stool is an indicator for a blockage in bilirubin processing and thus potential liver dysfunction.

Bilirubin test:
Total/Unconjugated/Conjugated forms.
Measurement of total bilirubin includes both unconjugated (indirect) and conjugated (direct) forms of bilirubin. Unconjugated bilirubin is a breakdown product of heme and since it is very hydrophobic, it is mainly transported bound to albumin that is circulating in the blood. The liver is responsible for clearing the blood of unconjugated bilirubin. The hepatocytes of the liver take up the unconjugated bilirubin and conjugate it to make it more water soluble. The
Conjugated bilirubin is then secreted into the bile and flows to the intestine. In the intestine some of the conjugated bilirubin can be reabsorbed. **Increased total bilirubin causes jaundice.** Increased blood bilirubin levels/jaundice can indicate a number of problems depending on the reason for the bilirubin buildup. The main categories include:

- **Prehepatic jaundice:** Due to excess production of bilirubin from excess RBC breakdown. Some causes include hemolytic anemias and internal hemorrhage.
  - Hemolytic anemias causes: Toxins, infections, other blood disorders.
- **Hepatic jaundice:** Due to liver damage, which is reflected as deficiencies in bilirubin metabolism - reduced ability of the hepatocytes to conjugate bilirubin. Some causes include cirrhosis and viral hepatitis.
- **Extrahepatic jaundice or Post hepatic jaundice:** Due to obstruction of the bile ducts, reflected as deficiencies in bilirubin excretion. Obstruction can be located either within the liver or in the bile ducts. Some causes include blockage of bile drainage by gallstones or cancer of the pancreas.
- **Neonatal:** Due to liver not being fully mature – may take a week or so of development.

If total bilirubin level is elevated then the levels of unconjugated and conjugated bilirubin can be used to determine the patient’s disorder.

- If unconjugated bilirubin (indirect bilirubin) is elevated then the problem is upstream of bilirubin conjugation in the liver. Hemolysis, viral hepatitis, or cirrhosis can be suspected.
- If conjugated bilirubin (direct) bilirubin is elevated, then the liver is conjugating bilirubin normally, but is not able to excrete it. Bile duct obstruction by gallstones or cancer should be suspected.

Where do the terms indirect (unconjugated) bilirubin and direct (conjugated) bilirubin come from? Bilirubin circulates in the bloodstream in two forms that include unconjugated and conjugated bilirubin. Bilirubin can be measured as total bilirubin level and/or as conjugated and unconjugated levels. More commonly, the laboratory uses a chemical test to detect the amount of conjugated bilirubin which is the water-soluble form of bilirubin, termed direct bilirubin because it is “directly” measuring the value. By subtracting this from the total bilirubin, an indirect estimate (indirect bilirubin) of unconjugated bilirubin is obtained.

**Prothrombin time (PT)**
The liver makes prothrombin and other proteins that are essential to normal blood clotting. **Prothrombin time is a test of the time it takes for a blood sample to clot.** If low levels of clotting factors are present, the prothrombin time is longer. Prothrombin time increases (blood takes longer to clot) in people with severe liver disease because the liver fails to make normal amounts of certain clotting factors.