

## **LIVER PHYSIOLOGY**

The liver has many important functions in maintaining the physiologic balance of the human body. The most important of these functions include:

- 1) **Digestion:** The liver excretes bile salts into the intestines. Bile aids the digestion of fats by emulsifying the fat molecules to facilitate their suspension in water, as well as by promoting the absorption of fats from the intestinal lumen into the cells lining the intestine and eventually the blood.
- 2) **Excretion of bilirubin:** Red blood cells last for about 120 days at which time they are destroyed by the spleen. Hemoglobin (the protein which is the primary carrier of oxygen in the red blood cells) is broken down by the liver into bilirubin, and then excreted by the liver into the intestines with the bile, where it is eventually eliminated from the body.
- 3) **Detoxification and/or excretion of drugs and hormones:** The kidneys generally have difficulty removing certain types of chemicals from the blood. There are many substances which are first modified by the liver before being excreted by the kidney. Other substances are modified by the liver and then excreted by the liver into the bile. Included among the substances excreted by the liver are various hormones, such as the steroids. The liver is also a major organ in the excretion of calcium.
- 4) **Carbohydrate metabolism:** All blood from the intestines flows from the intestines through the liver. The liver performs many functions related to maintaining an appropriate glucose level, including the conversion of other simple sugars from the diet into glucose, the production of glycogen, and the conversion of some amino acids into glucose. The liver also uses some of the byproducts of carbohydrate metabolism to form various chemical compounds necessary for other physiologic functions.
- 5) **Fat metabolism:** The liver is a major organ in the processing of dietary fat and the conversion of stored fat into products more readily used for energy. In particular, the liver is responsible for removing the triglycerides and fatty acids circulating in our blood after a meal and converting them to fats for storage. Also a large amount of the cholesterol used by our body is formed in the liver, and the liver is also the major site for production of fats from carbohydrates and proteins.
- 6) **Protein metabolism:** The liver's role in protein metabolism is probably the most important of its metabolic functions. The liver functions to remove the nitrogen groups from amino acids, form urea from the excess ammonia produced in that process (the urea is excreted by the kidneys), form various proteins (especially albumin which helps regulate the amount of fluid in the blood vessels, and some of the proteins that are essential to blood coagulation) that circulate in the blood, and form some amino acids for protein production.

## **PRIMARY BILIARY CIRRHOSIS**

Primary biliary cirrhosis (PBC) is a serious disease of the liver in which the intrahepatic bile ducts become scarred and blocked. This impairs the ability of the liver to excrete bile into the gastrointestinal tract. There follows a buildup of bilirubin in the tissues resulting in the clinical condition known as jaundice. With this decreased excretion of the bile, there tends to be a buildup of copper in the body, but the exact mechanism for this finding is unknown.

Though the initial disease affects the excretory function of the liver, the blockage of the bile ducts can eventually cause damage to the liver cells, thereby impairing the other functions of the liver relating to synthesis of proteins, metabolism of glucose and fats, and detoxification of chemicals. This advanced stage of disease is known as cirrhosis and is characterized by:

- 1) Derangements in excretory function: Bilirubin levels in the blood increase; estrogen levels increase (often causing proliferation of small blood vessels in the skin to form spider angiomas); an accumulation of copper in the liver and other organs, though the exact mechanism for this is unknown.
- 2) Breakdown of liver cells: Certain enzymes normally found in the liver cells are released into the blood including alkaline phosphatase and SGOT. The presence of high quantities of these enzymes in the blood is then used to diagnose liver damage.
- 3) Derangements in protein formation: Albumin levels in the blood are decreased; the decrease in albumin allows more fluid to leave the blood and enter the tissues causing edema (swelling); proteins necessary for blood coagulation are not formed causing it to take longer for blood to clot (as measured by prothrombin time); proteins necessary for the production of platelets are decreased.
- 4) Portal hypertension: The scarring of the liver affects the flow of fluids through the liver. The liver becomes enlarged (hepatomegaly); albumin leaks into the peritoneum causing tissue to accumulate (ascites).
- 5) Derangements in fat metabolism: Cholesterol and triglyceride levels in the blood are affected as the liver does not remove the fats absorbed into the blood from the intestines.

## THE CLINICAL TRIAL

The causes of PBC are unknown, though there is some suggestion that it has an auto-immune component. The disease affects women more than men, and is most often first diagnosed between the ages of 35 and 60. In some patients, the disease is asymptomatic, however in those patients developing signs and symptoms of liver disease, death usually occurs within 5-10 years of first diagnosis.

A randomized clinical trial of d-penicillamine in the treatment of PBC was conducted at the Mayo Clinic. This drug was considered experimentally due to its action in aiding the excretion of copper and its activity in auto-immune processes. The data from this clinical trial are given in the file Liver.data according to the format described below. Data is available on multiple covariates which can be used to assess the severity of the disease for the trial participants at the time they entered the study (i.e., at randomization or baseline).

### *Demographic:*

age = subject's age at randomization  
sex = indicator that subject is female

### *Hepatocellular damage (measured by enzymes released by damaged liver cells):*

alkphos = serum level of alkaline phosphatase  
sgot = serum level of SGOT

### *Liver inflammation and cirrhosis:*

hepmeg = indicator of hepatomegaly (enlarged liver)  
ascites = indicator of fluid accumulation in abdominal cavity  
platelet = count of platelets circulating in blood (portal hypertension)  
stage = pathologic staging of disease

### *Lack of liver function:*

bili = level of bilirubin in blood  
protime = time to clot blood (malabsorbed vit K and no clotting factor)  
albumin = level of albumin (a protein) in blood  
edema = indicator of swelling in legs (from low blood proteins)  
edmadj = a measure of edema adjusted for prior treatment  
cholest = serum cholesterol level (decreased fat metabolism)

triglyc = serum triglycerides (decreased fat metabolism)  
spiders = indicator of spider angiomata (from excess of estrogens)

*Idiopathic:*

urinecu = level of urinary copper

The following variables measure the treatment assignment and treatment outcome:

*Treatment:*

treatmnt = indicator of treatment group

*Outcome:*

obstime = time until death or last follow-up

status = indicator that a death was observed

We desire to use this data to assess whether d-penicillamine is effective in prolonging the survival of patients with PBC.

### THE DATA FILE

The ASCII file liver.txt contains the data for 418 patients with primary biliary cirrhosis. 312 of these patients were randomized to receive either D-penicillamine or placebo in the clinical trial. Limited data is available on the other 106 patients. Each row of the file corresponds to a single patient.

The variables measured in the datasets are as follows:

age	Age in years
albumin	Serum albumin
alkphos	Serum alkaline phosphatase
ascites	Presence of ascites (fluid accumulated in peritoneum)
bili	Serum bilirubin
cholest	Serum cholesterol
edema	Presence of edema (swelling of extremities)
edmadj	A graded measurement of edema (0.5= treated or minimal edema)
hepmeg	Presence of hepatomegaly (enlarged liver)
obstime	Observation time in days
platelet	Platelet count
protime	Prothrombin time
sex	Sex (0=male, 1=female)
sgot	Serum SGOT
spiders	Presence of spider angiomata
stage	Stage of disease (1= best, 4= worst)
status	Survival status (0=censored)
treatmnt	Treatment group (1=drug,2=placebo)
triglyc	Serum triglycerides
urinecu	Urine copper

The file can be read into Stata using the command (type it all on one line until Stata gives a continuation line):

```
infile age albumin alkphos ascites bili cholest edema edmadj hepmeg obstime  
platelet protime sex sgot spiders stage status treatmnt triglyc urinecu using  
liver.txt
```

The file can be read into S-plus using the command:

```
liver <- scan("Liver.data",list(age=0,albumin=0,alkphos=0,ascites=0,bili=0,
cholest=0,edema=0,edmadj=0,hepmeg=0,obstime=0,platelet=0,protime=0,
sex=0,sgot=0,spiders=0,stage=0,status=0,treatmnt=0,
triglyc=0,urinecu=0))
```