Lecturer: Dr. Ameen M. Al-Juboori
E-mail: AmeenAL-Juboori@mustaqbal-college.edu.iq

Lecture # 10

The Liver and Its Artificial Replacement

Introduction:

The liver is a vital organ present in vertebrates and some other animals that is necessary for survival. It has a wide range of functions, including detoxification, protein synthesis, and production of biochemicals necessary for digestion. Currently, there is no way to compensate for the absence of liver function in sustaining life.

The liver plays a major role in metabolism, that is, digestion, and has a number of functions in the body, including glycogen storage, decomposition of red blood cells, plasma protein synthesis, hormone production, and detoxification. It lies below the diaphragm in the thoracic region of the abdomen. It produces bile, an alkaline compound that aids in digestion, via the emulsification of lipids. The liver's highly specialized tissues regulate a wide variety of high-volume biochemical reactions, including the synthesis and breakdown of small and complex molecules, many of which are necessary for normal vital functions. Medical terms related to the liver often start with hepato- or hepatic from the Greek word for liver.

It is a reddish-brown organ with four lobes of unequal size and shape. A human liver normally weighs between 1.4–1.6 kg (3.1–3.5 lb) and is a soft, pinkish-brown, triangular organ. It is both the largest internal organ (the skin being the largest of all organs) and the largest gland in our body.

It is located in the right upper quadrant of the abdominal cavity, resting just below the diaphragm. The liver lies to the right of the stomach and overlies the gallbladder. It is connected to two large blood vessels: the hepatic artery and the portal vein. The hepatic artery carries blood from the aorta, whereas the portal vein carries blood containing digested nutrients from the small intestine and the descending colon. These blood vessels subdivide into capillaries, which then lead to a lobule. Each lobule is made up of millions of hepatic cells, which are the basic metabolic cells.

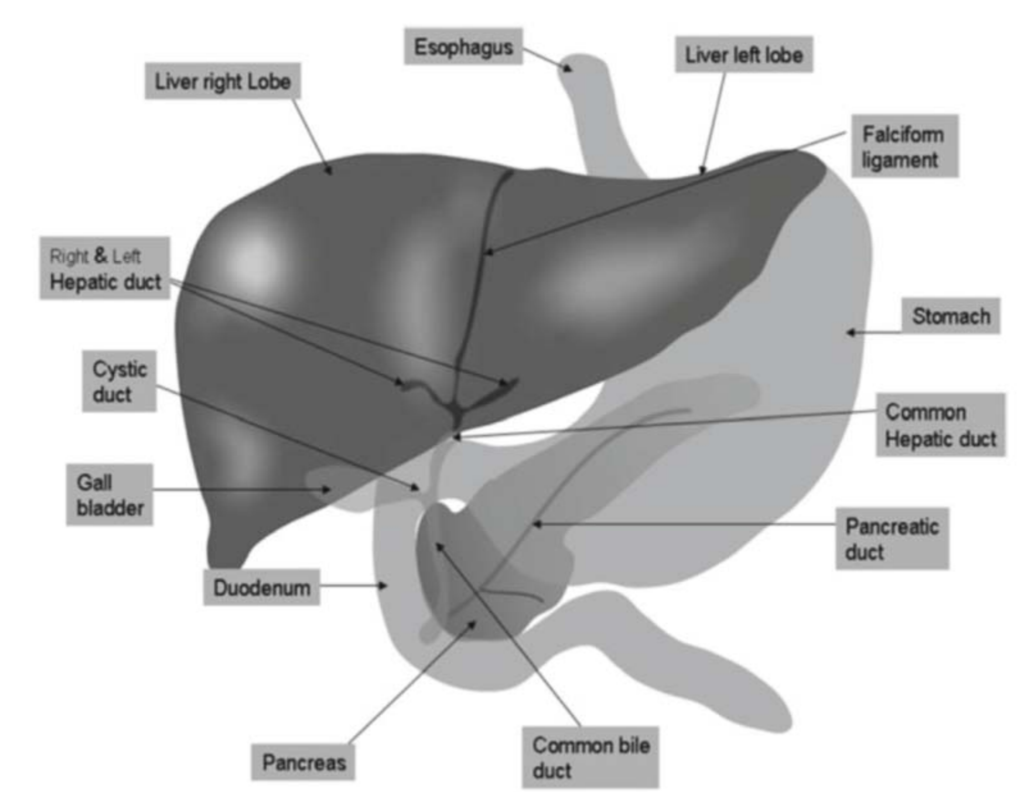

Figure 1: Anatomical features of a human liver

Bioartificial Liver Device

A bioartificial liver device (BAL) is an artificial extracorporeal supportive device for an individual who is suffering from acute liver failure.

Currently, the purpose of BAL-type devices is not to permanently replace liver functions, but to serve as a supportive device , either allowing the liver to regenerate properly upon acute liver failure, or to bridge the individual's liver functions until a suitable transplant is obtained.

Function

BALs are essentially bioreactors, with embedded hepatocytes (liver cells) that perform the functions of a normal liver. They process oxygenated blood plasma, which is separated from the other blood constituents . Several types of BALs are being developed, including hollow fiber systems and flat membrane sheet systems.

Hollow Fiber System

One type of BAL is similar to kidney dialysis systems that employ a hollow fiber cartridge. Hepatocytes are suspended in a gel solution, such as collagen, which is injected into a series of hollow fibers. In the case of collagen, the suspension is then gelled within the fibers, usually by a temperature change. The hepatocytes then contract the gel by their attachment to the collagen matrix, reducing the volume of the suspension and creating a flow space within the fibers. Nutrient media is circulated through the fibers to sustain the cells. During use, plasma is removed from the patient's blood. The patient's plasma is fed into the space surrounding the fibers. The fibers, which are composed of a semipermeable membrane, facilitate the transfer of toxins, nutrients, and other chemicals between the blood and the suspended cells. The membrane also keeps immune bodies, such as immunoglobulins, from passing to the cells to prevent an immune system rejection.

Comparison to Liver Dialysis

The advantages of using a BAL over other dialysis-type devices (e.g., liver dialysis) is that metabolic functions (such as lipid and plasma lipoprotein synthesis, regulation of carbohydrate homeostasis, production of serum albumin and clotting factors, etc.), in addition to detoxification, can be replicated without the use of multiple devices. There are several BAL devices currently in clinical trials.

A series of studies in 2004 showed that a BAL device reduced mortality by about half in acute liver failure cases. The studies, which covered 171 patients in the U.S. and Europe, compared standard supportive care to the use of a bioreactor device using pig liver cells.

Progress Toward an Artificial Liver Transplant

Liver transplantation is currently the only available treatment for severe liver failure, but there aren't enough donors to fill the need. Researchers have now made transplantable liver grafts for rats that may point the way toward a successful liver transplant substitute for humans.

Our liver's job is to help fight infections and clean our blood. It also helps digest food and stores energy for when we need it. People needing a liver transplant in the U.S. are placed on a national waiting list kept at the United Network for Organ Sharing. Their blood type, body size, and severity of sickness all play a role in when they'll receive a liver. Whole livers can be donated only from people who have just died. Currently, there's an estimated shortfall of about 4,000 livers per year. It may be much higher in India.

Liver cell transplantation has shown some promise but has limited uses. To be successful, an artificial transplant must be sufficiently large to provide enough liver function. That requires a network of small blood vessels—called a microvascular network—to transport oxygen and nutrients throughout the structure.

Decellularization is the process of removing cells from a structure but leaving a scaffold with the architecture of the original tissue. It has shown some success in other organs. One group of scientists reported the decellularization of an entire heart that preserved the original architecture and microvascular network. A research team led by Dr. Korkut Uygun at Massachusetts General Hospital tried a similar approach for the liver; the work was supported by NIH's National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) and others.

In the June 13, 2010, online edition of Nature Medicine , Dr. Uygun and his team explained the process they developed. They used a gentle detergent over three days to decellularize the liver while preserving its structure. A matrix of proteins remained behind to hold the liver's shape. Using a dye, the researchers showed that the microvascular network in each eerily translucent liver was intact.

The researchers were then able to successfully introduce functional hepatocytes, i.e., liver cells, back into the matrix. When they tested the recellularized matrix, they found that it carried out liver-specific functions at levels comparable to a normal liver. Grafts transplanted into rats maintained their functional hepatocytes as well, for a few hours. The researchers noted, however, that successful engineering of an entire functional liver will require other types of cells.

Researcher Dr. Colin McGucklin and co-workers at Newcastle University say that pieces of artificial liver could be used to repair livers injured by disease, alcohol abuse, or other causes. These artificial livers could also be used outside the body in a manner analogous to the dialysis process used to keep alive patients whose kidneys have failed.

In next 10 years' time, entire livers could be grown in the lab and then be transplanted into human beings. The stem cells used by Drs. McGucklin and his team in their research are gathered from umbilical cords ("cord blood"), seen by some as a more ethical alternative to stem cells created from human embryos.

The cells are then placed in a Bioreactor , a device developed by NASA to simulate the weightless environment of space. The cells are situated in a growth medium that is constantly rotated, putting the cells in an endless state of free-fall. Ordinary cell growth in a nutrient medium in a dish does not provide a culture environment that supports three-dimensional tissue assembly. Epithelial cells without a three dimensional assembly environment lack the proper clues for growing into the variety of cells that make up a particular tissue. Epithelial cells are the basic cells that differentiate tissue into specific organ functions. In a rotating Bioreactor, scientists can fool cells into behaving as though they are in a body.